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BKK: Commercializing a New Drug

The Decision

Dr. Brad Worthington and his friend, Thurman Ballard, needed to pull the trigger on a business decision.[1] The choice was agonizing. It was January 2018, and Worthington had spent most of the last 18 years developing, using in his anesthesia practice, and teaching others how to use BKK, his unique and proprietary formulation of nonopioid anesthesia drugs. Worthington had created BKK by combining three other drugs approved by the US Food and Drug Administration (FDA)—bupivacaine, ketorolac, and ketamine—to form a locally infiltrated pain reliever at the surgical site that worked for up to 40 hours.[2] Bupivacaine was a local anesthetic sometimes used as a nerve block; ketorolac was a nonsteroidal anti-inflammatory drug (NSAID); and ketamine was a common anesthesia drug with a long and safe history. When ketamine was administered in subanesthetic doses,[3] it was currently the best-known drug for pain relief. The unique combination in BKK had many benefits. It prevented nausea and inflammation—inflammation was the cause of a significant portion of a surgical patient's pain—and worked so well that it greatly reduced and often eliminated the patient's need to take opioid pain relievers during and after surgery. Some peers found it hard to believe, but even patients who had undergone complicated back, neck, and joint surgeries, which normally required one- or two-night inpatient stays, reported reduced opioid use and went home shortly after surgery. Many patients did not need any opioids after their procedures.

The BKK patent, which was based on the unique antinausea effects of Worthington's combination method, had just been issued several months prior. Now, Worthington, Ballard, and other close consultants had to choose from among three paths to commercialization, which they had researched over the past year. In the first path, they could work with an institutional investor to fund the millions of dollars required to pursue a New Drug Application (NDA) with the FDA, then market BKK as a new chemical entity, a new drug. This path was likely to confer more protection than the current patent, which established BKK as a new formulation of existing approved drugs that documented a unique antinausea benefit—but the NDA carried with it risks as well. Second, Worthington and Ballard could choose to partner with a compounding pharmacy to produce and

[1] This is a partially disguised, field-based case. All information and quotations, unless otherwise noted, derive from author interviews with company representatives conducted on November 15 and 27 and December 6, 2018. Some names, including those of companies, company representatives, and conferences, have been disguised.

[2] Locally infiltrated meant that the surgeon injected the properly combined formulation directly into the patient's surgical sites rather than administering the drugs to the patient's bloodstream via an intravenous drip. This meant the pain medication was delivered only where it was needed to accomplish the surgery, rather than to the patient's entire body. The exact duration of analgesic effectiveness remained unknown. Patients often reported post-operatively that the BKK admixture (combining multiple multimodal mechanisms of action) appeared to provide a benefit measured in days and not hours.

[3] Subanesthetic meant a dose lower than one that would normally cause a patient to lose consciousness, as was often desired during but not after surgery.

This field-based case was prepared by Rebecca Goldberg, Guest Executive Lecturer, Darden School of Business; and G. Paul Matherne (MD, MBA '10), Adjunct Professor, Darden School of Business, and Dammann Professor of Pediatrics and Service Line Lead, University of Virginia Children's Hospital.

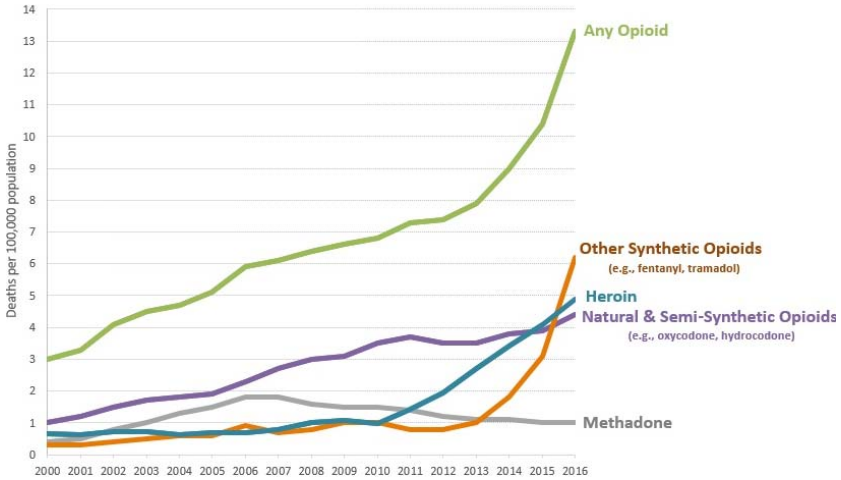
market BKK as a combination drug, which would require no additional FDA approval but would require expensive analytic testing. Third, they could develop and market a convenience kit, which was a box containing the three component drugs—bupivacaine, ketorolac, and ketamine—that were separately bottled in the correct amounts, along with directions for safely admixing and administering BKK at the point of care. Should they take on investors and wait out the lengthy 18- to 24-month FDA approval process? Or should they forego the additional layer of patent protection and get to market sooner with one of the other two more immediate options, using the patent they had today?

The Opioid Crisis

One of Worthington's personal goals in his surgical practice was to reduce opioid exposure and possible dependency in as many people as possible at an affordable price. He knew that after just 1 day of opioid use, 6% of patients were still taking opioids a year later, and that after just 8 days of postsurgical opioid use, that likelihood increased to 13.5%. Of patients taking opioids for more than 31 days, 29.9% were still doing so after one year. As reported in a 2017 study, "Approximately 1 in 7 persons who received a refill…were on opioids 1 year later."[4] Heroin users overall were, on average, in their early 20s and any gender. They tended to live in more rural areas (75.2%), and 3 out of 4 (75.0%) had been introduced to opioids through prescription drugs.[5]

Of the 63,632 fatal drug overdoses in the United States in 2016, almost 40,000 were the direct result of an opioid—either prescription or illicit—with a sharp rise in deaths due to illicitly manufactured fentanyl. As compared to 2015 data, opioid-related fatal overdoses increased across all racial, ethnic, socioeconomic, geographic, and gender groups, with deaths from synthetic opioids doubling, deaths from prescription opioids increasing 10.6%, and heroin fatalities increasing 19.5%.[6] These increases continued long-term trends in opioid use throughout the 2000s (see **Figure 1**).

Figure 1. Overdose deaths involving opioids, by type of opioid, United States, 2010 to 2016.



Source: "Timeline Graph of Overdose Deaths Involving Opioids," CDC, part of the United States Department of Health and Human Services; as a work of the US federal government, the image is in the public domain. Uploaded by "Timeshifter," March 20, 2017, https://commons.wikimedia.org/wiki/File:Timeline_Overdose_deaths_involving_opioids,_United_States.jpg, original at https://www.cdc.gov/drugoverdose/images/data/opioid_deaths_multicolor.gif (both accessed Dec. 19, 2018).

[4] Anuj Shah, Corey J. Hayes, and Bradley C. Martin, "Characteristics of Initial Prescription Episodes and Likelihood of Long-Term Opioid Use—United States, 2006–2015," Morbidity and Mortality Weekly Report, Centers for Disease Control and Prevention (CDC), March 17, 2017, https://www.cdc.gov/mmwr/volumes/66/wr/mm6610a1.htm (accessed Dec. 19, 2018).

[5] T. J. Cicero, M. S. Ellis, H. L. Suratt, and S. P. Kurtz, "The Changing Face of Heroin Use in the United States: A Retrospective Analysis of the Past 50 Years," *JAMA Psychiatry* 71, no. 7 (July 1, 2014): 821–26, https://www.ncbi.nlm.nih.gov/pubmed/24871348 (accessed Dec. 19, 2018).

[6] "U.S. Drug Overdose Deaths Continue to Rise; Increase Fueled by Synthetic Opioids," CDC press release, March 29, 2018, https://www.cdc.gov/media/releases/2018/p0329-drug-overdose-deaths.html (accessed Dec. 19, 2018).

Annual costs related to the opioid epidemic in the United States continued to be a massive burden, estimated in 2013 at $78.5 billion. Of that amount, $28.9 billion was attributed to health care and substance abuse treatment, with an additional significant amount in criminal justice costs.[7] Another study, published by the US president's Council of Economic Advisers in 2017, used a different evaluation method called the "value of a statistical life," which was based on assessments of the economic valuations of fatality risk reduction. This study pegged the 2015 costs related to lives lost due to opioid overdoses in the United States at $200 billion to $500 billion.[8] Opioid abuse also correlated with increased health care costs at the individual level. Surgical patients with a diagnosis of opioid abuse or dependence tended to stay in the hospital after surgery 50% longer and cost around $2,000 more per event than the general population, and they were readmitted to the hospital within 30 days at a 20% greater rate.[9] And there were documented increased costs associated with surgical opioid use among the general population. In a 2010 study of almost 40,000 general surgery patients, those who received opioids and experienced a single opioid-related adverse event—such as nausea, vomiting, constipation, rash, itching, mental changes, or depressed respiration—had significantly higher costs and risks than those who did not experience such an event; specifically, they had 55% longer initial hospital stays, 47% overall higher costs of care, 36% increased risk of 30-day readmission, and 340% higher risk of inpatient mortality.[10]

Opioid exposure in the clinic and hospital had become the new hospital-acquired condition. Hospitals often felt compelled to develop opioid stewardship programs. Knowing this, Worthington developed and promoted a program for BKK called "DREAMS," which stood for drinking, eating, and mobilizing. These activities were considered an important part of patient care and postoperative recovery.

For all of these reasons, Worthington felt it was his personal obligation as a doctor to explore nonopioid alternatives for his patients. He was an inspiring, energetic person, and he was optimistic about BKK's potential to reduce pain and opioid dependency. In his words:

> Despite the need for improved postoperative analgesia and despite the dramatic increase in opioid use I've seen over the years, our patients were still in pain. Our patients deserve better, and there are simple answers that save money and save lives. The solution was simple. The "solution" was BKK.

Beginning in 2000, while Worthington was the medical director and chief of anesthesia of an ambulatory surgery center, he tried a variety of FDA-approved nonopioid drugs available to him, in an effort to identify the best possible combinations to manage his patients' surgical and postsurgical pain and to limit opioid use during recovery. During this period, he discovered the combination now known as BKK.

Early Development: 2000–11

From 2000 to 2005, Worthington was the medical director and chief of anesthesia at the Howell-Allen Clinic, the Saint Thomas Outpatient Neurosurgery Center in Nashville, Tennessee. The innovative facility, which was part of Saint Thomas Health Care Services and an affiliated division of the parent company,

[7] Curtis Florence, Feijun Luo, Likang Xu, and Chao Zhou, "The Economic Burden of Prescription Opioid Overdose, Abuse and Dependence in the United States, 2013," *Medical Care* 54, no. 10 (October 2016): 901–6, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5975355/ (accessed Dec. 19, 2018).

[8] "The Underestimated Cost of the Opioid Crisis," report of the Council of Economic Advisers, Office of the President (November 2017), 6.

[9] A. Gupta, J. Nizamuddin, D. Elmofty, S. L. Nizamuddin, A. Tung, M. Minhaj, A. Mueller, J. Apfelbaum, and S. Shahul, "Opioid Abuse or Dependence Increases 30-day Readmission Rates after Major Operating Room Procedures: A National Readmissions Database Study," *Anesthesiology* 128, no. 5 (May 2018): 880–90, https://www.ncbi.nlm.nih.gov/pubmed/29470180 (accessed Dec. 19, 2018).

[10] E. R. Kessler, M. Shah, S. K. Gruschkus, and A. Raju, "Cost and Quality Implications of Opioid-Based Postsurgical Pain Control Using Administrative Claims Data from a Large Health System: Opioid-Related Adverse Events and Their Impact on Clinical and Economic Outcomes," *Pharmacotherapy* 33, no. 4 (April 2013): 383–91, https://www.ncbi.nlm.nih.gov/pubmed/23553809 (accessed Dec. 21, 2019).

Ascension Health, was an ambulatory surgery center (ASC) and the first freestanding neurosurgical center in the United States. Worthington managed two operating rooms (ORs) and eight acute care rooms (ACRs). In 2005, the facility physically moved from an ambulatory setting to become a fully equipped acute-care hospital in a freestanding office tower connected to a larger tertiary care hospital. This new and larger location included 6 ORs and 22 ACRs; better sterilization and lab support at the new hospital enabled more invasive and complex spinal procedures. The new acute care facility then became the Saint Thomas Hospital for Specialty Surgery.

Worthington first used BKK when providing anesthesia for lumbar laminectomies,[11] for which the historic average length of stay (LOS) in 2000 was one to three days. With the implementation of protocols for BKK and other changes he made to his standard opioid-free processes and procedures, he reduced this to a routine three-hour LOS, from admission to discharge. Astonishingly, the LOS even for complex spinal procedures was so reduced that the facility risked losing reimbursement at the higher hospital rate by some insurers, like Medicaid, which deemed that the surgeries performed would be reimbursed at the hospital rate only if they resulted in an LOS of at least two nights. Over time, Worthington broadened the types of surgeries offered at his hospital to include traditional inpatient neurosurgical spine procedures, multilevel cervical and lumbar fusions, and joint replacements—for which BKK was used exclusively. Again, even these more complicated surgeries could be performed with an overnight stay or even same-day discharge. By 2018, BKK had been used safely and effectively in over 120,000 consecutive surgeries.

While many of the surgeons practiced exclusively at the Hospital for Specialty Surgery, some surgeons also performed procedures in other facilities. Worthington developed USP-797-compliant procedures (admixing and regulatory procedural standards adopted by all state Boards of Pharmacies) for admixing and using BKK in his hospital, and instructed these surgeons in how to correctly and safely use his techniques on their patients. Many surgeons asked if they could use BKK at other hospitals. Worthington said,

> I wasn't even thinking about patenting BKK in 2010. I told these surgeons, yes, you can use BKK at the other facilities where you work, but only for your own patients. I wouldn't want anyone at another facility to have a problem with BKK, especially if I didn't give them permission to use it and train them in the proper procedures. I only wanted our surgeons to use BKK if they followed the USP-797 criteria and followed the clinical safe-use guidelines I developed. This is how other facilities got the "recipe" for BKK. Surgeons in practices incorporating BKK routinely called its use a "game changer" for them as far as both effective pain management and avoidance of opioid exposure.

Formative Events: 2012 to Early 2016

Between 2012 and 2016, several events occurred that had an impact on Worthington's ability to bring BKK to market. The New England Compounding Center (NECC) disaster occurred; Worthington initiated the patenting process; and he met Ballard, who later became his commercialization consultant and close friend.

The NECC disaster

Until 2012, the compounding pharmacy business in the United States was an industry without significant FDA regulation or oversight. In 2012, an avoidable error occurred at NECC: a spinal injectable compound containing a fungal contaminant was released to patients, causing fungal meningitis.

[11] According to the Mayo Clinic, "A lumbar laminectomy is surgery that creates space by removing the lamina—the back part of a vertebra that covers your spinal canal. Also known as decompression surgery, laminectomy enlarges your spinal canal to relieve pressure on the spinal cord or nerves." "Laminectomy," Mayo Clinic, https://www.mayoclinic.org/tests-procedures/laminectomy/about/pac-20394533 (accessed Dec. 23, 2018).

The Department of Justice reported:

> A 131-count criminal indictment was unsealed today in Boston in connection with the 2012 nationwide fungal meningitis outbreak, the Justice Department announced. Barry J. Cadden, owner and head pharmacist of New England Compounding Center (NECC) and NECC's supervisory pharmacist Glenn A. Chin were charged with 25 acts of second-degree murder in Florida, Indiana, Maryland, Michigan, North Carolina, Tennessee and Virginia.
>
> The outbreak was caused by contaminated vials of preservative-free methylprednisolone acetate (MPA) manufactured by NECC, located in Framingham, Massachusetts. The U.S. Centers for Disease Control and Prevention (CDC) reported that 751 patients in 20 states were diagnosed with a fungal infection after receiving injections of NECC's MPA. Of those 751 patients, the CDC reported that 64 patients in nine states died.
>
> "Those who produce and sell the drugs that we take have a special responsibility to make sure that they prepare those drugs under suitable conditions, and that what leave their facilities is safe," said Acting Assistant Attorney General Joyce R. Branda for the Justice Department's Civil Division. "The indictment charges that the defendants' conduct in this case was corrupt and carried out with a complete disregard to the public health. The department's Consumer Protection Branch along with our law enforcement partners is steadfast in our commitment to use every criminal and civil tool at our disposal to hold accountable those who are willing to put our lives at risk in the reckless pursuit of their profits."[12]

These events prompted a new law regulating compounded drugs made by pharmacies. The law defined the manufacturing and reporting practices of compounded drugs, how they could be marketed and distributed, and how they were to be inspected. This new Drug Quality and Security Act was signed into law on November 27, 2013, and established section 503B in the Federal Food, Drug, and Cosmetic Act.[13]

Worthington began to wonder if, now that consistent safety and accountability standards had been put in place, he could identify a 503B compounding pharmacy partner to safely manufacture BKK. He also noticed that many hospitals that had previously compounded their own medications in-house were now exploring outsourcing arrangements with FDA-accredited and -inspected compounding manufacturing facilities. For the first time, he began to think there might be a way to safely bring BKK to market.

The patenting process

In late 2013, just after the 503B process was promulgated, Worthington retained a West Coast patent attorney to help him initiate the patenting process. His attorney was also a pharmacologist and an intellectual property attorney for the University of California and University of Arizona medical systems. Because all three of BKK's component drugs were already patented, Worthington needed to identify the unique benefits conferred by his specific formulation in order to justify a new patent. The attorney recommended to

[12] "14 Indicted in Connection with New England Compounding Center and Nationwide Fungal Meningitis Outbreak," US Department of Justice, Office of Public Affairs, press release, December 17, 2014, https://www.justice.gov/opa/pr/14-indicted-connection-new-england-compounding-center-and-nationwide-fungal-meningitis (accessed Dec. 22, 2018).

[13] "Information for Outsourcing Facilities," US Food and Drug Administration, https://www.fda.gov/drugs/guidancecomplianceregulatoryinformation/pharmacycompounding/ucm393571.htm (accessed Dec. 23, 2018).

Worthington that they file a provisional patent while they determined how to best express those unique benefits.[14]

Worthington's patent was set to publish in late 2017. However, during the due diligence process, his patent firm located "a mention of the term BKK" in another doctor's blog, dated 2004. This minor and seemingly innocent mention of "BKK" in the public record might indicate prior art,[15] and thus detract from Worthington's case that he was the sole developer of BKK and its related protocols. As a result of this potential roadblock, his attorney advised him to file a continuation on the basis of an experimental exemption, which was common practice in the pharmaceutical industry.

Meeting Thurman Ballard

In early 2015, Worthington met Ballard, an independent consultant in the health care industry. At the time, Ballard was working with investors who were building and staffing the new Carolina Coast Surgery Center (CCSC). Worthington liked him immediately, and began working with him and the other investors to launch the CCSC facility and to develop the operating protocols, taking on the role of Chief Medical Officer (CMO). In this capacity, Worthington established BKK as the anesthesia standard in broad use for all operations conducted at CCSC, including orthopedic, hernia, plastic, breast, gall bladder, and other specialty surgeries.

Between 2013 and 2016, other hospitals beyond those in Worthington's purview began to show widespread adoption of BKK, mixing it in batches under an in-house hood and delivering it to surgeons at the point of care. They used USB-797 protocols, but Worthington knew he would also need to pursue current good manufacturing process (cGMP) compliance to assure his invention was used in the safest manner available.

Working with Ballard: August 2016 to February 2018

Between August 2016 and February 2018, Worthington and Ballard worked together to make significant strides toward bringing BKK to market. They were invited to conduct a product pitch to a group purchasing organization (GPO) supplying products and services to Medical Leaders in Healthcare (MLH), one of the nation's largest hospital systems, and the BKK patent was published. Also, during this time, three major pharmaceutical companies began development of long-acting multimodal anesthesia products that were similar in many ways to BKK.

Pitching AngelHealth

In August 2016, Worthington and Ballard were invited to speak about the opioid crisis at HealthNow, a large health industry symposium. Worthington recalled of his speech:

> I told them: Because of BKK, I haven't given an intravenous opiate or benzodiazepine since 2000. I use nonopioid analgesics and adjuvants, induce anesthesia, and the operation begins. As the surgical wounds are closed, BKK is infiltrated directly into the patient's wounds in a specific way. And 80% of the time when the patient wakes up, they are ambulatory in less than 45 minutes—many times ready for discharge in less than an hour. We've had patients meet discharge criteria after 10 minutes. Occasionally we prescribe oral opioids for one to two days for rescue. It's as close to opioid free as you can get. And the audience said, "When can you get this to us?"

[14] A provisional patent was sometimes referred to as a "placeholder patent" because it established the filer as being first to file, which conferred protection to the filer as the details of the patent process were worked out with the US Patent Office.

[15] "Prior art" was a legal term that, in the context of determining ownership of intellectual property, included all information available to the public that may have had bearing on the originality of the subject under review. Prior art could prevent a new patent application from being approved if it indicated that another person or entity had independently arrived at the same ideas.

Later, at the event, Worthington saw Tommy Sigfried, CMO of AngelHealth and a neurosurgeon with whom Worthington had worked, limping across the room. When Worthington asked him what had happened, Sigfried replied that he had recently had knee surgery and said, "I sure wish they had BKK when they did *my* surgery! Why don't you come pitch this product to our product team? I'd love to learn more about it." Worthington knew that AngelHealth had previously been a division of MLH, and that it was still the GPO for MLH. He also knew that Sigfried was already familiar with BKK and had seen its benefits in his own patients. Worthington was ecstatic! What an opportunity.

Barely a month later, Worthington and Ballard returned to AngelHealth to pitch BKK, along with a compounding pharmacy partner with which they had discussed initial terms. The plan was that the compounding pharmacy partner would manufacture BKK to supply MLH's requirements. AngelHealth would market and distribute the product, and manage the relationship. It seemed like a great way to launch. They would incur a $100,000 up-front legal cost, borne by Worthington, and additional manufacturing setup costs of around $400,000, which would also be borne by Worthington as a loan against receivables. Even with these up-front costs, Ballard had forecasted that this amount would be recouped within one month of production due to a handshake agreement for a 20,000 initial unit purchase from Sigfried and an estimated ongoing weekly order of 2,000 units. At $16 per dose and a $61 fixed sale price, the initial cash outlay seemed to be an excellent investment. The team planned to bring BKK to market after a delay of about three months while the compounding pharmacy conducted the required clinical, packaging, and shelf-life studies, and then set up the production lines.

Because of the FDA guidelines for marketing of compounded pharmaceutical products, there was a chance that MLH and AngelHealth would be the only customers that BKK would ever acquire. BKK was a product that was ordered and administered by the surgeon or surgical team. The best approach to selling it would be through medical device sales representatives, but the FDA prohibited actual sales representatives from marketing and promotion of compounded products.

At the pitch meeting, representatives from AngelHealth appeared excited about BKK and what it could offer MLH and its patients. Working with the compounding pharmacy, on the other hand, was more problematic. The pharmacy delayed communicating a timeline for production, and without a product or launch date, Worthington and Ballard weren't able to nail down a concrete arrangement with AngelHealth. They weren't sure of the underlying reasons, but wondered if they would need to identify a different compounding pharmacy or 503B manufacturer as a manufacturing partner, or whether they would encounter the same delays across the board with compounding pharmacies.

Patent approval

In late 2016 and early 2017, after examining the data he had accumulated over the years and on the advice of his counsel, Worthington augmented his patent filing. As a point of differentiation, he cited BKK's greatly reduced instances of nausea and vomiting as compared to other anesthesia drugs. With most general anesthetics, there was a 30%–80% chance of vomiting, but with BKK, that chance was reduced to just 0.186%.[16] It was on this basis that his patent was approved, first as a provisional patent in August 2017, and then as an approved patent in October 2018. Four years and $150,000 in legal fees later, Worthington was now the owner of BKK.

[16] Chance of vomiting with non-BKK anesthetics based on Tong J. Gan, Pierre Diemunsch, Ashraf S. Habib, Anthony Kovac, Peter Kranke, Tricia A. Meyer, Mehernoor Watcha, Frances Chung, Shane Angus, Christian C. Apfel, Sergio D. Bergese, Keith A. Candiotti, Matthew Chan, Peter J. Davis, Vallire D. Hooper, Sandhya Lagoo-Deenadayalan, Paul Myles, Greg Nezat, Beverly K. Philip, and Martin R. Tramer, "Consensus Guidelines for the Management of Postoperative Nausea and Vomiting," *Anesthesia and Analgesia* 118, no. 1 (January 2014): 85–113, https://journals.lww.com/anesthesia-analgesia/Fulltext/2014/01000/Consensus_Guidelines_for_the_Management_of.13.aspx (accessed Feb. 6, 2019). Chance of vomiting with BKK based on internal company research.

The patent protected the combination and production methods for mixing and administering BKK, but it did not provide protection for BKK as a new drug. That type of patent, an NDA, would require an up-front investment of at least $2.5 million to cross the first FDA approval hurdle, and, if approved, another $10 million–$25 million immediately afterward to complete the approval process. The whole process would take 18 to 24 months and require significant resources and institutional capabilities that Worthington and Ballard, acting alone, did not have.

Exparel and the nonopioid market

Most hospitals at the time were using Exparel as a locally injected analgesic that was intended to reduce the need for postsurgical opioids, but its effectiveness was variable. It also cost $300 a dose—three times the price point that Worthington and Ballard planned for BKK. Exparel had been approved by the FDA in 2011 and was marketed by Pacira Pharmaceuticals as a long-acting liposomal bupivacaine product. While Exparel's FDA label stated that the bupivacaine release should provide pain relief for 72 hours, some anecdotal evidence disputed this. Some surgeons who were able to use BKK at some facilities but were required to use Exparel at others reported to Worthington that they used far fewer narcotics when using BKK.

Sales of Exparel exceeded $280 million in 2017,[17] as it was the only commercially available option for long-acting, locally infiltrated analgesia. Pacira projected Exparel sales to continue to grow, as the demand for minimizing opioid use and opioid-sparing alternatives was projected to grow in every surgical subspecialty.

Mylan Pharmaceuticals, Heron Therapeutics, and Durect Corporation were then all in the pipeline stages of development and approval for their own bupivacaine-based long-acting infiltrative analgesics. A summary of BKK's potential competition can be viewed in **Table 1**. These alternatives were all targeted as replacements for Exparel, and were anticipated to offer a 72-hour therapeutic window. One industry consultant reported to Ballard she was aware of an intended price point in the $300 per-dose range.

[17] Pacira Pharmaceuticals, Inc. SEC Form 10-K, 2017, p. 51.

Table 1. Summary of potential competitor drugs.

Company	Drug	Mechanism of Action	FDA Approval Status
Heron Therapeutics, Inc.	HTX-011	Bupivacaine and meloxicam. Combined local anesthetic and NSAID. Website stated "reduces local inflammation and reverses the acidic environment caused by surgery, allowing enhanced penetration of bupivacaine into the nerves and potentiating its effect."	Investigational. Granted Fast Track Designation from the FDA in the fourth quarter of 2017 and Breakthrough Therapy Designation from the FDA in the second quarter of 2018. Potential approval no earlier than fourth quarter 2019.
Mylan N.V.	Meloxicam	Intended for acute pain, for example, during dentistry procedures, postsurgery, and with orthopedic defects. Meloxicam also proposed to treat chronic pain.	Mylan purchased the rights to develop and sell from Prayog Labs LLC as announced on April 11, 2018. Planned to submit NDA application.
Durect Corporation	POSIMIR	Website stated, "POSIMIR is an investigational nonopioid analgesic being evaluated for its ability to provide 3 days of continuous local pain relief after surgery. Intended for administration just once at the close of surgery, POSIMIR may be instilled directly into the surgical incision(s) with a blunt-tipped applicator or injected into targeted anatomic spaces under endoscopic guidance. Once placed, clinical and nonclinical studies have shown it to form a biodegradable depot that releases bupivacaine directly to the surgical site at a stable rate for 72 hours."	Phase 3 clinical trials began in November 2015. In October 2017, the trial was reported to not show the required results. However, in two previous late-stage trials, the efficacy was more clearly demonstrated. Durect was working to understand the trial results better, so FDA approval was delayed, with no further information available.
Trevena Inc.	Oliceridine	Intravenous therapy modulated the body's mu opioid receptors to relieve pain without the respiratory and gastrointestinal side effects that limited other agents, according to the company.	In a pair of Phase II trials, Trevena's drug was more effective than a placebo and as effective as morphine in postsurgery patients, notching significantly lower rates of vomiting, nausea, and breathing problems compared with morphine. Awarded "breakthrough therapy" status with FDA to fast-track approval.

Sources: "HTX-011," Product Portfolio, Heron Therapeutics, https://www.herontx.com/HTX-011 (accessed Jan. 12, 2019); "Mylan to Leverage Its World-Class Scientific Platform to Develop a Novel Delivery for Meloxicam, a Non-Opioid Pain Medication," Mylan N.V. press release, April 11, 2018, http://newsroom.mylan.com/2018-04-11-Mylan-to-Leverage-its-World-Class-Scientific-Platform-to-Develop-a-Novel-Delivery-for-Meloxicam-a-Non-Opioid-Pain-Medication (accessed Jan. 12, 2019); "POSIMIR (bupivacaine extended-release solution)," Pipeline Investigational Products, Durect, http://www.durect.com/pipeline/development/posimir/ (accessed Jan. 12, 2019); "Oliceridine Injection Development," Trevena, Inc. Pipeline Portfolio, http://www.trevena.com/Oliceridine-development.php (accessed Feb. 18, 2019).

Annually in the United States, there were 15 million surgical procedures for which a long-acting locally infiltrated nonopioid analgesic like BKK was considered to be ideally suited. These surgeries fell into four major specialties, including orthopedic, general, OB/GYN, and plastic surgery. The postoperative pain market for these 15 million procedures was theoretically expected to be $4.9 billion.[18]

Worthington was convinced that BKK lasted longer than Exparel, was far less expensive to manufacture, and showed more consistent multimodal analgesic results. While the competitor products in development were expected to last for 72 hours and BKK lasted for only 40 hours, in Worthington's extensive experience, BKK was so effective that it negated the need for additional opioid pain medication. He felt it was critical to bring BKK to market before the FDA approved these other drugs so that he could control the context of the conversation in the health care market about these nonopioid alternatives. The length of time that the drug was able to provide pain relief was, he felt, less important than how well it worked and the overall reduction in opioid use after surgery.

Exploring Commercialization Options

To commercialize BKK, Worthington and Ballard needed to find either an institutional partner to complete the NDA process or a manufacturing company that would be able to reliably produce, distribute, and market BKK, following all safety and regulatory procedures. To accomplish this, Worthington had established a new company, Hutchison Health, Inc. (HH). He and Ballard also researched and assessed three commercialization options: taking on investors and pursing an NDA, locating a new compounding pharmacy partner, or manufacturing a convenience kit.

Option 1: NDA

The first option they considered was to seek an institutional investment partner to fund the NDA process. Doing so would confer additional patent protection and provide institutional support for marketing, production, and distribution. Ballard and Worthington met with several interested private equity investors, who generally offered similar terms. The investors wanted 10% equity in HH in exchange for the first $2.5 million, to be used to pass the first NDA hurdle, followed by another 50%–60% of HH in exchange for $10 million–$25 million, to be used to pass the second and final NDA hurdle and bring the product to market, leaving Worthington with 35% ownership. Ballard estimated the production cost per dose, using this pathway, at $32, with a price point of $135–$150. Sales for this option were expected to be the highest, at 650,000 the first year with a 36% year-over-year growth rate—after the approval, which could take 18–24 months or several years.

This path was not without risks. While a successful NDA offered more patent protection, it also exposed HH to greater potential litigation costs, and Worthington might lose control of his lifelong work. More capital might need to be placed in escrow to account for that possibility. BKK combined bupivacaine with an NSAID, and most of the potential competing drugs then in development leveraged a similar combination. Worthington and Ballard worried that patent challenges and lawsuits from the big pharmaceutical world would inhibit BKK's commercialization and overall success.

Taking on investors and an institutional pharmaceutical partner would bring resources, connections, and capabilities, but it also meant assuming the related risks. These new partners had their own priorities and would make their own decisions. And, of course, there was the possibility that the NDA might not succeed. Last,

[18] Heron Therapeutics Inc. SEC Form 8-K, March 19, 2018, p. 5, https://herontherapeutics.gcs-web.com/static-files/cecc4343-53ca-4c6a-b010-2b24d5331641 (accessed Jan. 9, 2019).

although they expected to qualify for an expedited NDA process, the 18- to 24-month lead time would also delay their path to market.[19] The three pharmaceutical companies that were also developing long-acting nonopioid analgesics had each made progress, and according to an industry expert close to Ballard, their products were also estimated to be 18–24 months away from entering the market. Taking all of these risk factors into account, Worthington and Ballard assessed the probability of success for this path at 50%.

Option 2: Find a compounding pharmacy partner

The second option Worthington and Ballard considered was to establish a partnership with a compounding pharmacy to produce and market BKK as a combination drug. Unfortunately, the compounding pharmacy with which they had partnered to pitch BKK to AngelHealth had encountered delays in setting up the production line. They considered whether to pursue a manufacturing arrangement with another compounding pharmacy, and expected that similar terms could be agreed upon with another partner. With any pharmacy, they expected a start-up time of about three months. One other drawback to this approach was that since the laws governing compounding drugs had changed, compounding pharmacies were limited in how they could market their products. Traditional pharmaceutical sales were not allowed; rather, compounded products could only be described from physician to physician, as if one colleague were advising another on best practices. The 503B-distribution pathway was direct from the manufacturer to the facility, with no middle distribution or storage. This might present some benefits. Worthington and Ballard did have a reasonable expectation that AngelHealth would bring their product to MLH, which was a large account.

Because of the federal restrictions on marketing and promotion of compounded drugs, they thought they would see a moderate annual growth rate of less than 10%, with annual revenues possibly reaching $10 million–$15 million within five years, but afterward remaining relatively flat. They assessed their probability of success for this option at 85%.

Option 3: Convenience kit

A third option, which a potential investor suggested to Worthington in the summer of 2016, was developing and marketing a convenience kit. The kit would be a container with the three component drugs—bupivacaine, ketorolac, and ketamine—separately bottled in the correct amounts, along with directions to the surgeon for mixing and administering BKK. This type of packaging had the benefit of a longer shelf life, because once BKK was mixed, it needed to be used within a certain period, while the individual drugs were more stable when stored separately. Marketing a convenience kit of three FDA-approved drugs was also not limited to conversations between physicians, but rather could be conducted by sales representatives in a more traditional pharmaceutical sales model.

After establishing a conversation with a manufacturer who was equipped and accredited to produce and distribute convenience kits, Worthington and Ballard thought through the costs, risks, and potential upsides so they could compare this to the other two options. The convenience kit option was the most expensive, with a per-dose cost of $45—but had the benefit of no up-front costs. The per-dose unit cost contained within it a portion of the manufacturer's up-front cost to design the packaging, perform all necessary testing, produce the drugs and packaging, assemble the kit, conduct sales using an in-house B2B sales force, and distribute the product. Worthington would have no up-front cost and would control the sale price. He and Ballard predicted their first-year sales at approximately 100,000 units, with a 20% growth rate. They pegged the price point at about $88. The convenience kit manufacturer needed four months to conduct the necessary clinical and

[19] All three of the component drugs for BKK had long and safe clinical histories, and BKK held great promise as a good answer to the need for nonopioid analgesics, so they thought it was likely they would qualify for expedited status, thereby cutting short the potential three-to-six-year lead time to bring a new drug to market.

packaging testing and bring up the production line. Considering the risks associated with this option, Worthington and Ballard assessed a 75% chance of success.

Choosing a Path: February 2018

In February 2018, Worthington had to make a choice. He said of the decision:

> I was broke. I had used most of my retirement fund to do this and spent entire decades of my professional career pushing it forward. I had spent a total of $150,000 already, and I would soon have to spend another $25,000 on maintaining my current patent. But it was also my life's work, and it was all I wanted to do to bring BKK to the world and prevent the next generation from becoming exposed to opioids. Along the dimensions of cost, availability, and effectiveness, BKK was the answer. Thurman and I needed to commit to a path, and bring it to market.

Exhibit 1

BKK: Commercializing a New Drug

BKK Development Timeline

Year	Development Milestone
2000	Dr. Brad Worthington begins work on iterations of BKK to reduce surgical and postsurgical opioid use.
2010	Worthington begins using the BKK combination drug in regular use in his own facility, using strict, sterile procedures.
2012	US Department of Justice cites New England Compounding Center for contamination. 503B becomes the regulatory standard in the compounding industry.
October 2013	Worthington begins work on a provisional, first-to-file patent.
Late 2013	Worthington's facilities using BKK achieved the highest possible HCAPS Scores (Hospital Consumer Assessment of Healthcare Providers and Systems) and several national anesthesia-related awards.
Early 2015	Worthington meets Thurman Ballard while working on establishing operating procedures at the new Carolina Coast Surgery Center; these procedures include adopting BKK as the anesthesia standard in broad use for all operation types, including sports medicine, hernia care, plastic surgeries, general surgery, breast biopsies, and gall bladder surgery.
2016	Worthington begins teaching surgeons in his hospital how to use USB-797-compliant protocols to mix BKK in batches under an in-house hood.
August 2016	Worthington gives a talk at HealthNow convention with Ballard and is asked to pitch BKK to AngelHealth, a spinoff of the large Medical Leaders in Healthcare (MLH) hospital system and a general purchasing organization (GPO) supplying MLH with compounded drugs.
October 2016	Worthington and Ballard make pitch to AngelHealth to supply BKK commercially, working with a selected compounding pharmacy partner.
Fall/Winter 2016	Selected compounding pharmacy partner creates delay after delay, apparently not motivated to consummate the relationship and begin production.
First half of 2017	Worthington and Ballard begin to explore private equity options, meeting with multiple health care fund managers.
Summer 2017	A potential hospital customer suggests the convenience kit option during an exploratory business development conversation. Worthington and Ballard begin to evaluate this as a potential third option.
August 2017	Provisional patent is approved pending a response.
October 2017	BKK patent issued under the rationale of the unique antinausea properties gained by using the drugs in combination.
Late 2017/Early 2018	Two additional new long-acting local analgesics are in production at major pharmaceutical companies.
Early 2018	Worthington and Ballard conduct additional research to evaluate their commercialization options.

Source: Created by authors based on interviews conducted on November 15 and 27, 2018.