

McCarley James L  
Form 4  
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**STATEMENT OF CHANGES IN BENEFICIAL OWNERSHIP OF SECURITIES**

Filed pursuant to Section 16(a) of the Securities Exchange Act of 1934, Section 17(a) of the Public Utility Holding Company Act of 1935 or Section 30(h) of the Investment Company Act of 1940

(Print or Type Responses)

1. Name and Address of Reporting Person \*  
McCarley James L

2. Issuer Name and Ticker or Trading Symbol  
RTI INTERNATIONAL METALS INC [RTI]

5. Relationship of Reporting Person(s) to Issuer  
(Check all applicable)

(Last) (First) (Middle)  
C/O RTI INTERNATIONAL METALS, INC., 1550 CORAOPOLIS HEIGHTS ROAD, SUITE 500

3. Date of Earliest Transaction (Month/Day/Year)  
01/28/2011

\_\_\_\_ Director \_\_\_\_\_ 10% Owner  
 Officer (give title below) \_\_\_\_\_ Other (specify below)  
EVP - Operations

(Street)  
PITTSBURGH, PA 15101-2973  
(City) (State) (Zip)

4. If Amendment, Date Original Filed(Month/Day/Year)

6. Individual or Joint/Group Filing(Check Applicable Line)  
 Form filed by One Reporting Person  
 Form filed by More than One Reporting Person

**Table I - Non-Derivative Securities Acquired, Disposed of, or Beneficially Owned**

1. Title of Security (Instr. 3)	2. Transaction Date (Month/Day/Year)	2A. Deemed Execution Date, if any (Month/Day/Year)	3. Transaction Code (Instr. 8)	4. Securities Acquired (A) or Disposed of (D) (Instr. 3, 4 and 5)	5. Amount of Securities Beneficially Owned Following Reported Transaction(s) (Instr. 3 and 4)	6. Ownership Form: Direct (D) or Indirect (I) (Instr. 4)	7. Nature of Ownership (Instr. 4)
Common Stock	01/28/2011		A	6,027 A	\$ 0 (1) 6,458 (2)	D	

Reminder: Report on a separate line for each class of securities beneficially owned directly or indirectly.

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SEC 1474 (9-02)



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Part I

**Item 1: Business**

**BUSINESS**

**Our Company**

We are a growing specialty pharmaceutical company focused on the acquisition, development and commercialization of branded prescription products. Our primary target markets are hospital acute care and gastroenterology, which are characterized by relatively concentrated physician prescriber bases that we believe can be penetrated effectively by relatively small, targeted sales forces. Cumberland is dedicated to providing innovative products which improve quality of care for patients and address poorly met medical needs.

Our product portfolio includes Acetadote<sup>®</sup> (*acetylcysteine*) Injection for the treatment of acetaminophen poisoning, Caldolor<sup>®</sup> (*ibuprofen*) Injection, the first injectable treatment for pain and fever approved in the United States, and Kristalose<sup>®</sup> (*lactulose*) for Oral Solution, a prescription laxative. We market and sell our products through our dedicated hospital and gastroenterology sales forces in the United States, which together comprised more than 100 sales representatives and managers as of March 1, 2011. We are also partnering our products to reach international markets. Net revenues for the years ended December 31, 2010, 2009 and 2008 were \$45.9 million, \$43.5 million and \$35.1 million, respectively.

We have both product development and commercial capabilities, and believe we can leverage our existing infrastructure to support our expected growth. Our management team consists of pharmaceutical industry veterans experienced in business development, product development, commercialization and finance. Our business development team identifies, evaluates and negotiates product acquisition, in-licensing and out-licensing opportunities. Our product development team develops proprietary product formulations, manages our clinical trials, prepares all regulatory submissions and manages our medical call center. Our quality and manufacturing professionals oversee the manufacture of our products. Our marketing and sales professionals are responsible for our commercial activities, and we work closely with our third party distribution partner to ensure availability and delivery of our products.

We have been profitable since 2004, generating sufficient cash flows to fund our development and marketing programs. In 2009, we completed an initial public offering of our common stock to help facilitate our further growth. Our strategy includes maximizing the potential of our existing products and continuing to expand our portfolio of differentiated products. Our current products are approved for sale in the United States, and we are working with overseas partners to bring them to international markets. We also look for opportunities to expand into additional patient populations through new product indications, whether through our own clinical studies or by supporting investigator-initiated studies at reputable research institutions. We actively pursue opportunities to acquire additional late-stage development product candidates as well as marketed products in our target medical specialties. Further, we are supplementing these growth strategies with the early-stage drug development activities of Cumberland Emerging Technologies (CET), our majority-owned subsidiary. CET partners with universities and other research organizations to develop promising, early-stage product candidates, which Cumberland Pharmaceuticals has the opportunity to commercialize.

We were incorporated in 1999 and have been headquartered in Nashville, Tennessee since inception. Our website address is [www.cumberlandpharma.com](http://www.cumberlandpharma.com). We make available through our website, free of charge, our annual reports on Form 10-K, our quarterly reports on Form 10-Q, our current reports on Form 8-K and any amendments, as well as

other documents, as soon as reasonably practicable after

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their filing with the U.S. Securities and Exchange Commission, or SEC. These filings are also available to the public at [www.sec.gov](http://www.sec.gov).

**Our Strategy**

**Maximize sales of Acetadote and Kristalose**

Since its launch in June 2004, we have consistently grown product sales for Acetadote, our injectable treatment for acetaminophen poisoning. Net revenue from Acetadote sales grew from \$18.8 million in 2007 to \$35.1 million in 2010, a compound annual growth rate of 23%. In 2009, we expanded our hospital sales force in preparation for the launch of Caldolor, and are also leveraging this expansion to support Acetadote sales. In early 2011, we received FDA approval for a new formulation of Acetadote and have subsequently launched that new product. We are working to secure patent protection for this new formulation, which we believe could provide us with long term protection for the product.

Kristalose competes in the high growth U.S. prescription laxatives market which, based on data from IMS Health, had sales of approximately \$373 million in 2009. After acquiring exclusive U.S. rights to Kristalose in April 2006, we assembled an experienced, dedicated sales force and designed a new marketing program, re-launching the product in September 2006. We inherited this product on a downtrend and have been successful in halting that decline and moving toward growth by enhancing brand awareness and highlighting the product's many positive, competitive attributes.

**Successfully commercialize Caldolor**

We believe Caldolor, injectable ibuprofen, currently represents our most significant product opportunity based on the large potential markets for intravenous treatment of pain and fever, as well as clinical results for the product to date. In September 2009, we began marketing the product in the U.S. through our expanded hospital sales force. During 2010, we focused on obtaining formulary approval and stocking of the product at U.S. hospitals and other medical facilities. Beginning in the first quarter of 2011, we began working to increase that stocking as well as drive use of the product in those facilities. We hold international patent rights for Caldolor and, in connection with certain current and potential future international partners, are working to seek regulatory approval for and market Caldolor outside of the U.S.

**Continue to build a high-performance sales organization to address our target markets**

We believe that continuing to build our sales infrastructure will help drive prescription volume and product sales. We currently utilize two distinct sales teams to address our primary target markets: a hospital sales force for the acute care market and a field sales force for the gastroenterology market.

*Hospital market:* We promote Acetadote and Caldolor through our dedicated hospital sales team of 72 representatives and managers. This team addresses hospitals across the U.S., and is comprised of sales professionals with substantial experience in the hospital market. According to IMS Health, U.S. hospitals accounted for approximately \$31 billion, or 10%, of U.S. pharmaceutical sales in 2009. However, IMS also reports that only 2% of approximately \$21 billion total pharmaceutical industry promotional spending was focused on hospital-use drugs in 2009. The majority of promotional spending is directed toward large, outpatient markets on drugs intended for chronic use rather than short-term, hospital use. We believe the hospital market is underserved and highly concentrated, and that it can be penetrated effectively by a small, dedicated sales force without large-scale promotional activity.

*Gastroenterology market:* We promote Kristalose through a dedicated field sales force addressing a targeted group of physicians who are responsible for a majority of total retail Kristalose prescriptions nationally. By investing in our marketing program, we believe that we will be able to increase market share for Kristalose and that we will be equipped to promote any further gastroenterology product

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additions as well. Because the market for gastrointestinal diseases is broad in patient scope, yet relatively narrow in physician base, we believe it provides product opportunities but can be penetrated with a modest sales force.

**Expand our product portfolio by acquiring rights to additional products and late-stage product candidates**

In addition to our product development activities, we are also seeking to acquire products or late-stage development product candidates to continue to build a portfolio of complementary products. We focus on under-promoted, FDA-approved drugs as well as late-stage development products that address poorly met medical needs, which we believe helps mitigate our exposure to risk, cost and time associated with drug discovery and research. We plan to continue to target products that are competitively differentiated, have valuable trademarks or other intellectual property, and allow us to leverage our existing infrastructure. We also plan to explore opportunities to seek approval for new uses of existing pharmaceutical products.

**Develop a pipeline of early-stage products through CET**

In order to build our product pipeline, we are supplementing our acquisition and late-stage development activities with the early-stage drug development activities of CET, our majority-owned subsidiary. CET partners with universities and other research organizations to develop promising, early-stage product candidates, and Cumberland Pharmaceuticals has the opportunity to negotiate rights to further develop and commercialize them.

**Our Products**

Our key products include:

<b>Product</b>	<b>Indication</b>	<b>Delivery</b>	<b>Status</b>
Acetadote®	Acetaminophen Poisoning	Injectable	Marketed
Caldolor®	Pain and Fever	Injectable	Marketed
Kristalose®	Chronic and Acute Constipation	Oral Solution	Marketed

**Acetadote®**

Acetadote® is an intravenous formulation of N-acetylcysteine, or NAC, indicated for the treatment of acetaminophen poisoning. Acetadote, which has been available in the United States since Cumberland's 2004 introduction of the product, is currently used in hospital emergency departments to prevent or lessen potential liver damage resulting from an overdose of acetaminophen, a common ingredient in many over-the-counter pain relief and fever-reducing products. Acetaminophen continues to be the leading cause of poisonings reported by hospital emergency rooms in the United States, and Acetadote has become a standard of care for treating this potentially life-threatening condition.

Originally approved in January 2004, Acetadote received FDA approval as an orphan drug, which provided seven years of marketing exclusivity from date of approval. In connection with the FDA's approval of Acetadote, we committed to certain post-marketing activities for the product. Our first Phase IV commitment (pediatric) was completed in 2004 and resulted in the FDA's 2006 approval of expanded labeling for Acetadote for use in pediatric patients. Our second Phase IV commitment (clinical) was completed in 2006 and resulted in further revised labeling for the product with FDA approval of additional safety data in 2008. We completed our third and final Phase IV commitment (manufacturing) for Acetadote in 2010, which has culminated in the approval and launch of a new, next



generation formulation of the product.

In October 2010, we submitted a supplemental new drug application (sNDA) to the FDA for approval of a new formulation of Acetadote designed to replace the original formulation. The new formulation,

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which is the result of the aforementioned Phase IV commitment made to the FDA, addresses the FDA's safety concerns and contains no ethylene diamine tetracetic acid or other stabilization and chelating agents and is preservative-free. In January 2011, we received FDA approval and commenced U.S. launch activities for this new Acetadote product. The original formulation has been removed from FDA reference materials and we no longer manufacture it. We have filed a patent application with the U.S. Patent and Trademark Office to protect the proprietary new formulation.

In March 2010, we submitted another sNDA to the FDA for the use of Acetadote in patients with non-acetaminophen acute liver failure. The sNDA included data from a clinical trial led by investigators at the University of Texas Southwestern Medical Center indicating that acute liver failure patients treated with Acetadote have a significantly improved chance of survival without a transplant. The study showed that these patients can also survive a significant number of days longer without transplant, which would provide patients requiring transplant increased time for a donor organ to become available.

Acute liver failure is associated with a high mortality rate and frequent need for liver transplantation. Approximately half of acute liver failure cases are caused by acetaminophen poisoning while the other half result from a variety of causes including hepatitis and alcohol. Currently, transplantation of the liver is the only treatment for patients with liver failure not caused by acetaminophen overdose.

In May 2010, the FDA officially accepted the sNDA and granted a priority review with a response expected in September 2010. In August 2010, we announced that the FDA extended its review of the sNDA by three months, resulting in a new Prescription Drug User Fee Act (PDUFA) goal date in December 2010. In December, we received a Complete Response Letter from the FDA indicating that the agency had completed its review of the application and had identified additional items that must be addressed prior to approving the new indication. We are in discussions with the FDA to gain clarity on a pathway to approval for this indication to treat a critically ill patient population with few treatment alternatives. In addition to expanded labeling for Acetadote, we have requested additional exclusivity for the product in association with the potential new indication.

We are also supporting a number of investigator-initiated studies to explore other potential indications for Acetadote.

**Market for Acetadote**

Acetaminophen is one of the most widely used drugs for oral treatment of pain and fever in the U.S. and can be found in many common over-the-counter products and prescription narcotics. Though safe at recommended doses, the drug can cause liver damage with excessive use. According to the American Association of Poison Control Centers National Poison Data System, acetaminophen poisoning was the leading cause of toxic drug ingestions reported to U.S. poison control centers in 2008. In a study published in 2005 that examined acute liver failure, researchers concluded that acetaminophen poisoning was responsible for acute liver failure in over half the patients examined in 2003, up from 28% in 1998. While an estimated 48% of cases were due to the accidental use over several days, causing chronic liver failure, an estimated 44% of the cases were intentional overdoses, causing acute liver failure. According to the FDA, four grams of acetaminophen is the daily maximum dosage recommended for adults. Ingesting just eight grams of acetaminophen a day can cause serious complications, especially in people, whose livers are stressed by virus, medication or alcohol. When used in conjunction with opiates, acetaminophen can offer effective pain relief after surgery or injury; however, patients taking acetaminophen/opiate combination drugs on a chronic basis often eventually require increasing amounts to achieve the same level of pain relief, which can also lead to liver failure. In January 2011, the FDA initiated a campaign to heighten awareness of the potential toxicity associated with

acetaminophen and announced that it is asking manufacturers of prescription

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acetaminophen combination products to limit the maximum amount of acetaminophen in these products to 325 mg per tablet in an effort to reduce adverse events.

NAC is widely accepted as the standard of care for acetaminophen overdose. According to *The Medical Letter on Drugs and Therapeutics*, NAC is virtually 100% effective in preventing severe liver damage, renal failure and death if administered within eight to ten hours of the overdose. Throughout Europe and much of the rest of the world, NAC has been available in an injectable formulation for over 25 years. Until the 2004 approval of Acetadote, however, the only FDA-approved form of NAC available in the U.S. was an oral preparation. Many U.S. hospitals prepared an off-label, IV form of NAC from the oral solution to treat patients suffering from acetaminophen poisoning. For a number of these patients, an IV product is the only reasonable route of administration due to nausea and vomiting associated with oral administration. Given this market dynamic, we concluded that a medical need existed for an FDA-approved, injectable formulation of NAC for the U.S. market.

**Competitive Advantages**

We believe Acetadote offers clinical benefits relative to oral NAC including ease of administration, minimizing nausea and vomiting associated with oral NAC, accurate dosage control, shorter treatment protocol and reduction in overall cost of acetaminophen overdose management. Acetadote makes NAC administration easier to tolerate for patients and easier to administer for medical providers.

Acetadote also offers a significant cost benefit to both patient and hospital by reducing treatment regimen, usually from three days to one day. An independently conducted study of Acetadote as a cost-saving treatment for acetaminophen poisoning was published in the December 2009 issue of the peer-reviewed *Journal of Medical Economics*. The study concludes that Acetadote is a less costly treatment regimen than oral NAC in all evaluated scenarios. The cost differential between the use of oral NAC and Acetadote was shown to range between \$881 and \$2,259, and was primarily attributable to the time required to complete recommended treatment. Under approved therapeutic protocols, the oral product requires 72 hours to administer compared to 21 hours for Acetadote. Consequently, the use of Acetadote results in shorter hospital stays, resulting in substantial cost disparity between the treatments.

**Caldolor®**

Caldolor, our intravenous formulation of ibuprofen, was the first injectable product approved in the United States for the treatment of both pain and fever. The FDA approved Caldolor for marketing in the United States in June 2009 following a priority review. The product is indicated for use in adults for the management of mild to moderate pain, for the management of moderate to severe pain as an adjunct to opioid analgesics, and for the reduction of fever.

In September 2009, we successfully implemented the U.S. launch of Caldolor, with more than 100 experienced sales professionals promoting the product across the country. Caldolor is stocked at the major wholesalers serving hospitals nationwide, and is available in 400mg and 800mg vials. We are focused on securing formulary approval and stocking nationally for Caldolor. Our sales group is highly focused on meeting with members of hospital pharmacy and therapeutic committees to secure placement on committee agendas to continue growing widespread formulary approval.

Beginning in 2011, we are reaching out to a wider audience within hospitals to drive pull-through sales of Caldolor in facilities that have added the product to formulary. Our sales professionals are equipped with marketing documents which highlight key differentiating factors including the product's ability to be safely dosed not only post-operatively

but also at induction of anesthesia. We supported the publication of Caldolor clinical data in 2010, with results from those trials appearing in peer-reviewed journals as well as being presented at appropriate medical meetings around the country.

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We have worldwide commercial rights to Caldolor. We market Caldolor in the United States through our existing hospital sales force, and are partnering with third parties to reach markets outside the United States.

**The Market for Caldolor**

Therapeutic agents used to treat pain are known as analgesics. Physicians prescribe injectable analgesics for hospitalized patients who have high levels of pain, require rapid pain relief or cannot take oral analgesics. According to IMS, the U.S. market for injectable analgesics exceeded \$329 million, or 671 million units, in 2009. This market consists principally of generic opioids and the NSAID ketorolac.

Injectable opioids such as morphine, meperidine, hydromorphone and fentanyl accounted for approximately 622 million units sold in 2009. While opioids are widely used for acute pain management, they are associated with a variety of side effects including sedation, nausea, vomiting, constipation, headache, cognitive impairment, reduced GI motility and respiratory depression. Respiratory depression, if not monitored closely, can be deadly. Opioid-related side effects can warrant dosing limitations, which may reduce overall effectiveness of pain relief. Side effects from opioids can cause a need for further medication or treatment, and can increase lengths of stay in post-anesthesia care units as well as overall hospital stay, which can lead to increased costs for hospitals and patients.

Despite a poor safety profile, use of ketorolac, the only non-opioid injectable analgesic available in the U.S., has grown from approximately 38 million units in 2004, or 5% of the market, to approximately 48 million units in 2009, or 7% of the market, according to IMS Health. The FDA warns that ketorolac should not be used in various patient populations that are at-risk for bleeding, as a prophylactic analgesic prior to major surgery or for intra-operative administration when stoppage of bleeding is critical.

Caldolor is one of only two U.S.-approved injectable treatments for fever, with the other being an injectable acetaminophen product. Significant fever, generally defined as a temperature of greater than 102 degrees Fahrenheit, can cause hallucinations, confusion, convulsions and death. Hospitalized patients are subject to increased risk for developing fever, especially from exposure to infectious agents. Patients with endotracheal intubation, sedation, reduced gastric motility, nausea or recent surgery are frequently unable to ingest, digest, absorb, or tolerate oral products to reduce fever. Treatment for these patients ranges from rectal delivery of medication to physical cooling measures such as tepid baths, ice packs and cooling blankets.

**Clinical Development Overview**

We acquired from Vanderbilt University an exclusive, worldwide license to clinical trial data on the use of intravenous ibuprofen for treatment of hospitalized patients with severe sepsis syndrome, a complex inflammatory condition often resulting in high fever due to infection. Published in the *New England Journal of Medicine*, this data indicated that intravenous ibuprofen was effective in reducing high fever in critically ill patients who were largely unable to receive oral medication. Based upon data generated from this study, we met with the FDA to determine the requirements for gaining FDA approval of intravenous ibuprofen through a 505(b)(2) application. Following discussion with and recommendations by the FDA, we implemented a development program for Caldolor that was designed to obtain approval for a dual indication for the product management of pain and reduction of fever. We performed extensive formulation work resulting in a patented, proprietary product and conducted a number of clinical studies evaluating the safety and efficacy of Caldolor for treatment of pain and fever.



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More than 1,400 subjects, including over 800 receiving IV Ibuprofen, were studied in seven clinical trials supporting our new drug application (NDA) filing. Below is a summary of the clinical trials that supported the NDA and that are currently described in our package insert:

<b>Study name</b>	<b>Number of subjects</b>	<b>Setting</b>	<b>Study results</b>
Pharmacokinetic Study	36	Healthy volunteers	Similar PK parameters between oral and Caldolor
Adult Safety Study	12	Healthy volunteers	Safe and well-tolerated IV infusion of Caldolor
Sepsis Study IND 32803 <sup>(1)</sup>	455	Hospitalized patients with severe sepsis	Significant and sustained reduction of temperature in patients with high fever ( $p < 0.01$ ) <sup>(3)</sup>
Adult Malaria Fever Study	60	Hospitalized adult malaria patients	Significant reduction in temperature over 24 hours of treatment ( $p = 0.002$ )
Phase III Adult Fever Study <sup>(2)</sup>	120	Hospitalized adult febrile patients	Significant, dose-dependent, reduction in temperature supporting 400mg dose ( $p = 0.0003$ )
Phase III Adult Dose Ranging Pain Study <sup>(2)</sup>	406	Hospitalized adult abdominal and orthopedic post-operative patients	Dose-dependent, morphine sparing effect (22%) supporting 800mg dose Significant reduction in pain intensity scores (VAS) <sup>(4)</sup> over 24 hours of treatment ( $p = 0.001$ )
Phase III Adult Abdominal Hysterectomy Pain Study <sup>(2)</sup>	319	Hospitalized adult abdominal hysterectomy patients	Significant, morphine-sparing effect (19%, $p < 0.001$ )  Significant reduction in pain intensity scores (VAS) over 24 hours of treatment ( $p = 0.011$ )
Total	1,408		

(1) Study data licensed from Vanderbilt University; Cumberland report filed 2003



- (2) Pivotal Study
- (3) P-value <0.05 represents statistical significance
- (4) Visual Analog Scale

*Additional Studies*

Adult Orthopedic Pain Study: We initiated a Phase III pain study in post-operative adult patients who had undergone orthopedic surgical procedures. Patients, all with access to patient controlled analgesia (PCA) with morphine, were randomized to also receive either 800mg of Caldolor (multi-modal therapy) or placebo treatment (standard therapy) four times daily for up to five days. The first dose in this study

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was administered prior (pre-operatively) to the surgical procedure. The primary endpoint was reduction in patient pain intensity scores using VAS measured with movement.

We enrolled 185 patients in the safety population. There was a significant reduction in pain intensity scores using VAS. Patients receiving Caldolor reported a 26% greater reduction in pain intensity after 24 hours ( $p < 0.001$ ; with movement Area Under the Curve of VAS) compared to placebo. 24 hours after the first dose of Caldolor was administered patients receiving Caldolor reported a 32% greater reduction in pain at rest ( $p < 0.001$  at rest AUC-VAS) compared to placebo. In this study, we also investigated the efficacy of Caldolor in reducing morphine use by patients receiving the 800mg dose. There was a significant reduction in morphine use by those receiving 800mg of Caldolor after surgery and through hour 24.

**Adult Burn Study:** We conducted a multicenter, randomized, double-blind, placebo-controlled trial at five U.S. and international clinical sites, including hospital burn units and burn centers, to evaluate the safety and efficacy of Caldolor in treating fever and pain in hospitalized burn patients. Patients were administered 800mg of Caldolor every six hours for five consecutive days. The study raised no safety concerns and the medication was well tolerated. There was no difference in adverse effects between patients who received a placebo and those receiving Caldolor. The study evaluated 61 adult burn patients with second or third degree burns covering more than 10 percent total body surface area. Other participant criteria included an anticipated hospital stay of more than 72 hours and temperatures of 38.0 degrees Celsius (100.4 degrees Fahrenheit) or greater. Statistical significance was achieved for the primary endpoint of reducing fever in burn patients over the first 24 hours of treatment.

**Adult Pharmacokinetics Study:** We conducted a randomized, double-blind, placebo-controlled, single dose crossover study of the pharmacokinetics, safety and tolerability of Caldolor in healthy adult volunteers. Twelve subjects were randomized in equal proportions to receive a single dose of 800mg Caldolor, administered over five to seven minutes, and oral placebo administered concurrently, followed by a wash-out period of a single dose of 800mg oral ibuprofen and intravenous placebo given concurrently. There were no serious adverse events nor any adverse events classified as moderate or severe. The most common adverse event, which was classified as mild, was infusion site pain in three subjects. The results of the study indicate that the mean C<sub>max</sub> of Caldolor was approximately twice that of the oral dose and the median T<sub>max</sub> for Caldolor was 6.5 minutes compared to 1.5 hours for the oral product. The AUC was similar between the two products. Results from the trial demonstrate the effects of decreasing infusion time for Caldolor from the current package insert guideline of no less than 30 minutes to an infusion time of five to seven minutes.

### **Phase IV Required Pediatric Assessment**

The required pediatric assessment for the Caldolor NDA was deferred until 2011 for the treatment of fever and until 2012 for the management of pain. Two clinical studies are currently underway to address the Phase IV requirements. By conducting pediatric clinical studies and supplying requested data to the FDA, Cumberland has the opportunity to obtain up to an additional six months of marketing exclusivity for Caldolor. If results of these trials are not favorable, we would not be eligible for additional pediatric exclusivity; however, unfavorable pediatric results would not impact marketing status for use in adults.

No additional Phase IV commitments were assigned by the FDA.

### **Safety Summary**

Extensive use and worldwide literature support the strong safety profile of oral ibuprofen. Building on the oral safety profile, we have assembled an integrated IV ibuprofen safety database combining data from our clinical trials as well as previously published study data. We used this data to support our

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NDA filing and will continue to use and update the data as a part of our ongoing safety evaluation. In addition, this data will be used by our sales force and in our marketing materials to promote Caldolor.

In clinical trials supporting our proposed indications, no serious adverse events have been directly attributed to Caldolor. The number and percentage of all patients in pivotal studies who reported treatment emergent adverse events was comparable between IV ibuprofen and placebo treatment groups. Additionally, there have been no safety related differences between Caldolor and placebo involving side effects sometimes observed with oral NSAIDs, such as changes in renal function, bleeding events or gastrointestinal disorders.

### **Kristalose®**

Kristalose is a prescription laxative administered orally for the treatment of constipation. An innovative, dry powder crystalline formulation of lactulose, Kristalose is designed to enhance patient compliance and acceptance. We acquired exclusive U.S. commercialization rights to Kristalose in 2006, assembled a new dedicated field sales force and re-launched the product in September 2006 under the Cumberland brand. We direct our sales efforts to physicians who are the most prolific writers of prescription laxatives, including gastroenterologists, pediatricians, internists and colon and rectal surgeons.

### **Market for Kristalose**

Constipation is a common condition in the U.S., affecting approximately 20% of the population each year. While many occurrences are non-recurring, a significant number are chronic in nature and require some treatment to control or resolve. Constipation treatments are sold in both the over-the-counter (OTC) and prescription segments. The prescription laxative market has historically consisted of a few highly promoted brands including MiraLax® (polyethylene glycol 3350), which is now being sold as an OTC product, and Amitiza®, as well as several generic forms of liquid lactulose. According to data from IMS Health, the prescription laxative market had sales of approximately \$373 million in 2009.

### **Competitive Advantages**

Kristalose is the only prescription-strength laxative available in pre-measured powder packets, making it very portable. The drug dissolves quickly in four ounces of water, offering patients a virtually tasteless, grit-free and calorie-free alternative to liquid lactulose treatments. We believe that Kristalose has competitive advantages over competing prescription laxatives, such as fewer potential side effects and contraindications as well as lower cost. There are no age limitations or length of use restrictions for Kristalose, and it is the only osmotic prescription laxative still sampled to physicians.

In 2009, we completed a multicenter, randomized, open label, crossover patient preference study evaluating Kristalose compared to similar products in liquid forms. Over a 14-day period, 50 patients with a recent diagnosis of chronic constipation were administered both Kristalose and liquid lactulose in a crossover study. Patient preference was measured through survey responses collected at the end of the study. Overall, more patients preferred Kristalose, noting portability as a key differentiating feature. More patients also preferred the taste of Kristalose as well as the consistency compared to the syrup formulations. There was no significant difference in adverse effects between patients who took Kristalose and those taking liquid lactulose. We are also exploring opportunities to expand into new indications with Kristalose.

### **Early-stage product candidates**

Our pre-clinical product candidates are being developed through CET, our 85%-owned subsidiary. Cumberland Pharmaceuticals negotiates rights to develop and commercialize CET product candidates, and in conjunction with research institutions has obtained nearly \$1 million in grant funding from the National Institutes of Health to support the development of these programs.

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Four of the more advanced CET development programs are:

- Ø In collaboration with Vanderbilt University, we are currently developing a new palliative treatment for fluid buildup in the lungs of cancer patients. The product candidate is a protein therapeutic being designed to treat pleural effusion, a condition which occurs when cancer spreads to the surface of the lung and chest cavity, causing fluid to accumulate and patients to suffer shortness of breath and chest pain. An estimated 100,000 patients are affected by this condition each year. Vanderbilt University researchers believe they have found a method of treating this condition which may involve less pain, a higher success rate and faster healing time, resulting in significantly shorter hospital stays.
- Ø In collaboration with the University of Mississippi, we are developing a highly purified, injectable anti-infective used to treat fungal infections in immuno-compromised patients. This product candidate's active ingredient is currently FDA-approved in a different formulation, and while it is the therapeutic of choice for infectious disease specialists in treating such fungal infections, it can produce serious side effects related to renal toxicity, often resulting in dosage limitations or discontinued use. University of Mississippi researchers have developed what they believe is a purer and safer form of the anti-infective.
- Ø In collaboration with the University of Tennessee, we are currently developing a novel asthma therapeutic designed to prevent remodeling of airway smooth muscle to reduce asthmatic reaction in pediatric patients. Airway remodeling occurs when the cells or muscles that line the airway become inflamed and can result in decreased lung function. University of Tennessee researchers believe they have found a treatment that can reduce, or even prevent, asthma attacks in children.
- Ø CET previously entered into an agreement with Vanderbilt University to develop a novel treatment to improve renal function in patients with hepatorenal syndrome, a condition where kidneys fail suddenly due to cirrhosis of the liver. The product candidate may reduce renal blood flow in association with acute kidney failure. In the third quarter of 2010, Cumberland Pharmaceuticals entered into an option agreement with CET to assume the rights and responsibilities associated with the product candidate. We have commenced product manufacturing and submitted an investigational new drug application for the clinical evaluation of this product candidate.

### **BUSINESS DEVELOPMENT**

Since inception, we have had an active business development program focused on acquiring rights to marketed products and product candidates that fit our strategy and target markets. We source our business development leads through our senior executives and our international network of pharmaceutical and medical industry insiders. These opportunities are reviewed and considered on a regular basis by a multi-disciplinary team of our managers against a list of selection criteria. We have historically focused on product opportunities with relatively low acquisition, development and commercialization costs, employing a variety of deal structures.

We intend to continue to build a portfolio of complementary, niche products largely through product acquisitions and late-stage product development. Our primary targets are under-promoted, FDA-approved drugs with existing brand recognition and late-stage development product candidates that address unmet medical needs in the hospital acute care and gastroenterology markets. We believe that by focusing mainly on approved or late-stage products, we can minimize the significant risk, cost and time associated with drug development.

Through CET, we are collaborating with a growing list of reputable research institutions. Our business development team is responsible for identifying appropriate CET product candidates and negotiating with our university partners to secure rights to these candidates. Although we believe that these collaborations may be important to our business in the future, they are not material to our business at this time.

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**CLINICAL AND REGULATORY AFFAIRS**

We have in-house capabilities for the management of our clinical, professional and regulatory affairs. Our team develops and manages our clinical trials, prepares regulatory submissions, manages ongoing product-related regulatory responsibilities and manages our medical information call center. Team members have been responsible for devising the regulatory and clinical strategies and obtaining FDA approvals for Acetadote and Caldolor.

**Clinical development**

Our clinical development personnel are responsible for:

- Ø creating clinical development strategies;
- Ø designing and monitoring our clinical trials;
- Ø creating case report forms and other study-related documents;
- Ø overseeing clinical work contracted to third parties; and
- Ø overseeing CET grant funding proposals.

**Regulatory and quality affairs**

Our internal regulatory and quality affairs team is responsible for:

- Ø preparing and submitting NDAs and fulfilling post-approval marketing commitments;
- Ø maintaining investigational and marketing applications through the submission of appropriate reports;
- Ø submitting supplemental applications for additional label indications, product line extensions and manufacturing improvements;
- Ø evaluating regulatory risk profiles for product acquisition candidates, including compliance with manufacturing, labeling, distribution and marketing regulations;
- Ø monitoring applicable third-party service providers for quality and compliance with current Good Manufacturing Practices, Good Laboratory Practices, and Good Clinical Practices, and performing periodic audits of such vendors; and
- Ø maintaining systems for document control, product and process change control, customer complaint handling, product stability studies and annual drug product reviews.

**Professional and medical affairs**



Our clinical and regulatory team provides in-house, medical information support for our marketed products. This includes interacting directly with healthcare professionals to address any product or medical inquiries through our medical information call center. Prior to the launch of Caldolor, we expanded our medical affairs staff to support inquiries from medical professionals regarding the appropriate use of Caldolor as well as to support the efforts of our expanded hospital sales force. In addition to coordinating the call center, our clinical/regulatory group generates medical information letters, provides informational memos to our sales forces and assists with ongoing training for the sales forces.

## **SALES AND MARKETING**

Our sales and marketing team has broad industry experience in selling branded pharmaceuticals. Our sales and marketing professionals manage our dedicated hospital and gastroenterology sales forces, including more than 100 sales representatives and district managers, direct our national marketing

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campaigns and maintain key national account relationships. In January 2007, we converted our hospital sales force, which had previously been contracted to us by Cardinal Health Inc., or Cardinal, to Cumberland employees through our wholly-owned subsidiary, Cumberland Pharma Sales Corp.

Our gastroenterology-focused team was formed in September 2006 with our re-launch of Kristalose and is a field sales force addressing high prescribers of laxatives. This gastroenterology sales force was previously contracted to us by Ventiv Commercial Services, LLC, or Inventiv. In September 2010, we converted the field sales force to Cumberland employees as we had previously done with our hospital force.

Our sales and marketing executives conduct ongoing market analyses to evaluate marketing campaigns and promotional programs. The evaluations include development of product profiles, testing of the profiles against the needs of the market, determining what additional product information or development work is needed to effectively market the products and preparing financial forecasts. We utilize professional branding and packaging as well as promotional items to support our products, including direct mail, sales brochures, journal advertising, educational and reminder leave-behinds, patient educational pieces and product sampling. We also regularly attend targeted trade shows to promote broad awareness of our products. Our National Accounts group is responsible for key large buyers and related marketing programs. This group supports sales and marketing efforts by maintaining relationships with our wholesaler customers as well as with third-party payors such as Group Purchasing Organizations, Pharmacy Benefit Managers, Hospital Buying Groups, state and federal government purchasers and influencers and health insurance companies.