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PAIN MANAGEMENT TREATMENT MARKETS

Trends, Industry Participants, Product Overviews and Market Drivers

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1. Overview

1.1 Statement of Report

Pain management describes a particular set of drugs, analgesics, which are specifically used as therapeutics to control pain in the clinic. As pain affects [REDACTED] people worldwide, these drugs are one of the major segments of the central nervous system (CNS) therapies market. This TriMark Publications analysis focuses on the role of pain management drugs in clinical use and in drug development for acute pain, chronic pain, neuropathic pain and nociceptive pain. The report discusses drug development and targeted therapeutics, as well as their use in clinical trials. New approaches meant to aid in development of drugs for therapeutic use are emphasized. The study also analyzes almost all of the major, specialty and emerging companies known to be marketing, manufacturing or developing pain management treatment products in the U.S. and worldwide. Additionally, this review provides detailed tables, charts and figures with past and projected sales data for the U.S., Europe and other geographic regions.

1.2 About this Report

This report describes new biomarker technology platforms developed for the analyses of drug targets that are connected to the effectiveness of therapeutic agents in a clinical setting. The emphasis is on those companies that are actively developing and marketing new companion diagnostic tests for performing biomarker tests during drug development, as opposed to the more routine and clinically accepted companion markers that are manufactured and marketed by large diagnostic companies for routine clinical use. This review focuses on biotech and pharmaceutical companies who have new products and procedures for drug development.

1.3 Scope of the Report

This study emphasizes pharmaceutical and biotech companies that are actively developing new drug entities for pain management. It includes drug candidates in the clinical trial and the early drug development setting.

1.4 Objectives

This report will provide:

- An overview of the global market for drugs for pain management.
- Analyzes of global market trends and projections of compound annual growth rates (CAGRs) through [REDACTED].
- A breakdown of the market by chronic, acute and other categories of pain.
- A review of pain management, with various types of pain categories, e.g. acute pain, cancer pain, chronic pain, neuropathic pain and nociceptive pain.
- Discussion of strategic considerations, such as personalized medicine.
- Delineation of drugs approved by the Food and Drug Administration (FDA) for pain management, along with emerging therapies, and a discussion of the expected decrease in the market's growth rate because of a series of patent expiries during the next several years.
- Comprehensive profiles of key companies in the industry..

The main objectives of this review are:

- Discovering growing market opportunities in drug development by identifying high-growth applications in different pain management areas, with a major focus on the biggest and expanding markets.
- Focusing on global pharmaceutical industry development through an in-depth analysis of the major world markets for pain management drugs, including growth forecasts.

This report discusses the various market trends and opportunities in pain management drug development. The reader should consult other TriMark Publications reports at <http://www.trimarkpublications.com> for detailed discussions of

important individual market segments in the pharmaceutical market. For instance, TriMark provides a separate market report called, *Pharmacogenomics for Clinical Use and in Drug Development*, on the use of companion diagnostic tests in treatment selection for patients in the diagnostic sector.

This analysis answers the questions:

- How can pharmaceutical companies identify which agents need to be developed for a specific area of pain?
- Is the stratification of pain markets a reason to avoid targeted therapies?
- Which biotech companies are developing candidates that might be potential targets for licensing or acquisition?
- What are the latest developments in analgesic development with regard to drug development?
- What categories of new pain management drugs are likely to receive FDA approval in the near term?
- Which companies are utilizing cutting-edge technologies to develop, validate and market pain management drugs for clinical use in the drug development and clinical trial setting?
- What impediments still exist to incorporating promising analgesics into clinical trials?
- Which pain management drugs show the most promise for use in drug approval?
- How can regulatory oversight drive approval and adoption of new technologies?
- Which alliances show the greatest synergy in bringing valid candidates to drug development?
- Which shared technologies are driving the most encouraging development?
- What is the current FDA stance on pain management drugs and their potential to increase efficiency in the clinic?
- How will insurance companies react to the use of pain management for pre-disposition and personalized medicine?
- What is the FDA's Critical Path Initiative?
- What factors really speed up the approval process?
- What stages does a pain management drug need to go through for the FDA to consider it validated?
- What is the FDA viewpoint on pre-competitive cooperation on clinical studies?
- What are the key opportunities in pain management discovery, development and commercialization?
- What are the current obstacles in pain management implementation?
- How do business strategies, such as those relating to acquisition, drive drug development strategies?
- What is the right balance between using external partnerships and developing internal infrastructure?
- How might novel pain management development lead to acquisition strategies and their implications for deal making?
- What strategies help translate pain management drugs from preclinical to clinical development?
- In what class of drugs is the value of using pain management drugs in decision making the highest?
- How can major pharmaceutical companies co-develop biomarkers in a cost-sharing model for regulatory acceptance?

Key features of this report:

- Analysis of leading pharmaceutical and biotechnology companies and academic groups at the forefront of pain management drug discovery, validation and utilization.
- Examination of the key trends currently affecting the discovery and application of pain management drugs such as the development of molecular diagnostics and the application of valid, probable valid and exploratory biomarkers in drug discovery.
- Assessment of the pivotal role that biomarkers play in the development of new diagnostic devices both in conjunction with drugs as targeted therapies and in areas of unmet medical need.

1.5 Methodology

The author of this report holds a Ph.D. in medicinal chemistry from Brunel University as well as an MBA in finance from the Open University Business School. He has over twenty years of experience working in the pharmaceutical industry. The editor of this report holds a Ph.D. in biochemistry from the University of Minnesota and has had post-doctoral experience at the University of Connecticut School of Medicine. He has taught at Quinnipiac University

and the Tufts School of Medicine, and has been a senior scientist at Pfizer Pharmaceutical Laboratories in drug development. He also has many decades of experience in science writing and as a medical industry analyst. He has over thirty years of experience as a licensed clinical laboratory director, as well as extensive experience in senior level management positions in biotech and medical service companies.

Company-specific information is obtained mainly from industry trade publications, academic journals, news and research articles, press releases and corporate websites, as well as annual reports for publicly-held firms. Additional sources of information include non-governmental organizations (NGOs) such as the World Health Organization (WHO) and governmental entities such as the U.S. Department of Health and Human Services (HHS), the National Institutes of Health (NIH), the Food and Drug Administration (FDA) and the Centers for Disease Control and Prevention (CDC). Where possible and practicable, the most recent data available have been used.

Some of the statistical information was taken from Biotechnology Associates' databases and from TriMark's private data stores. The information in this study was obtained from sources that we believe to be reliable, but we do not guarantee the accuracy, adequacy or completeness of any information or omission or for the results obtained by the use of such information. Key information from the business literature was used as a basis to conduct dialogue with and obtain expert opinion from market professionals regarding commercial potential and market sizes. Senior managers from major company players were interviewed for part of the information in this report.

Primary Sources

TriMark collects information from hundreds of Database Tables and many comprehensive multi-client research projects, as well as Sector Snapshots that it publishes annually. TriMark extracts relevant data and analytics from its research as part of this data collection.

Secondary Sources

TriMark uses research publications, journals, magazines, newspapers, newsletters, industry reports, investment research reports, trade and industry association reports, government-affiliated trade releases and other published information as part of its secondary research materials. The information is then analyzed and translated by the Industry Research Group into a TriMark study. The Editorial Group reviews the complete package with product and market forecasts, critical industry trends, threats and opportunities, competitive strategies and market share determinations.

TriMark Publications Report Research and Data Acquisition Structure

The general sequence of research and analysis activity prior to the publication of every report includes the following items:

- Completing an extensive secondary research effort on an important market sector, including gathering all relevant information from corporate reporting, publicly available databases, proprietary databases, direct meetings and personal interviews with key personnel.
- Formulating a study outline with the assigned writer, including important items:
 - Market and product segment grouping and evaluating their relative significance.
 - Key competitors' evaluations including their relative positions in the business and other relevant facts to prioritize diligence levels and assist in designing a primary research strategy.
 - End-user research to evaluate analytical significance in market estimation.
 - Supply chain research and analysis to identify any factors affecting the market.
 - New technology platforms and cutting edge applications.
- Identifying the key technology and market trends that drive or affect these markets. Assessing the regional significance for each product and market segment for proper emphasis of further regional/national primary and secondary research.

- Launching a combination of primary research activities including two levels of questionnaires, executive-direct focused, company-specific, and region-specific communications to qualified and experienced senior executives worldwide.
- Completing a confirmatory primary research assessment of the report's findings with the assistance of Expert Panel Partners from the industry being analyzed.

1.6 Executive Summary

Pain is a major health issue that is estimated to affect [REDACTED] people worldwide. Chronic pain is highly debilitating but acute or episodic pain is also a major problem. Pain is also a physiological defense mechanism to damaging stimuli. Pain is generally perceived as a sensory phenomenon.

Drugs for the treatment of pain, called analgesics, are generally classified as CNS therapies. Pain management therapies constitute one of the major segments of the CNS market. The analgesic effects of opium and pure opioids such as morphine have long been recognized as the mainstay of treatment for many types of pain.

Pain comes in many forms, both acute and chronic, while some conditions such as cancer pain comprise both forms of pain. Migraine is a distinct form of acute pain with severe headaches a major symptom. Acute pain is also experienced as a consequence of injuries. Acute pain, which can last from several days to six months and covers arthritic conditions, represents 10% of the \$2 billion global analgesic market. Chronic, persistent pain may be associated with earlier injuries and is also commonly associated with musculoskeletal and joint conditions.

Chronic pain is common in older, arthritic, patients but is present in many other conditions, with an estimated 30 million Americans suffering from chronic pain. Opioids are ill suited to treating chronic pain because their long term use can give rise to a physiological dependence. Thus, arthritic pain is better suited to treatment with non-steroidal anti-inflammatory drugs (NSAIDs) and certain topical agents.

Neuropathic pain is a distinct form of chronic pain that arises as a consequence of lesions in, or dysfunctions of, the nervous system, and is generally long lasting. Common forms of neuropathic pain are diabetic neuropathy, postherpetic neuralgia and HIV-related neuropathic pain. These are estimated to affect over six million people in the major world markets. Neuropathic pain requires specific and targeted treatment, and is treated mainly with selected antidepressants and anticonvulsants.

Fibromyalgia is another common, chronic condition which appears to be a disorder of pain processing. Although substantially underdiagnosed, it is estimated to affect 1% to 2% of the adult population. Fibromyalgia only responds to a few specific drugs with few agents currently approved for its treatment.

Recommendations for the treatment of pain are based upon incremental use of more potent analgesics until pain relief is achieved. The three-step paradigm for treating chronic pain is well established. Similar approaches to treating neuropathic pain, trigeminal pain and fibromyalgia have been proposed but are less widely accepted to date. These approaches cover the use of a number of classes of drugs, each of which also has some side effect issues.

The most extensively used drugs are acetaminophen, NSAIDs and opioids. Overusage of acetaminophen poses problems of hepatotoxicity which can result in liver failure, leading the FDA to propose restrictions on the maximal amount of acetaminophen in combination products. NSAIDs increase bleeding time and damage the gastric mucosa, which can result in gastric ulceration. These problems are not seen with agents like celecoxib.

Opioids unfortunately have a constellation of unwanted multiple side effects. In addition to the development of physical dependence (addiction) to the drug, their use can produce sedation, dizziness, emesis, constipation and respiratory depression. The last named should be avoided because of the potentially fatal consequences. In addition, opioids are widely abused, which has led the development of tamper-proof formulations and to the imposition of additional controls on their availability, relative to most prescription drugs.

Despite the size of the world pain market and the availability of multiple classes of drugs whose analgesic use is well established, there are many unmet needs. There is a medical need for improved therapies for chronic pain, with respect to efficacy and/or side effect profile, and to address the widely recognized undertreatment of pain. The WHO has stated that undertreated pain is the number one health problem in North America, with the number of chronic pain patients in the U.S. exceeding the total of those suffering from diabetes, heart disease and cancer. A similar undertreatment of acute pain is also recognized while both neuropathic pain and fibromyalgia suffer from both undertreatment and under diagnosis. There is thus a considerable need for new, more effective pain therapeutics.

The global pain market is one of substantial value, despite the fact that there are few blockbuster analgesic products on the market. There is widespread usage of generic drugs and also significant reliance on over-the-counter drugs. In addition, there is significant off-label use of drugs to treat some pain conditions. Consequently, the reported values for the pain market vary substantially, although all agree it is of high value. In [REDACTED], the global pain market was estimated to be \$ [REDACTED], with \$ [REDACTED] of this produced in the seven major markets (the U.S., Japan, France, Germany, Italy, Spain and the UK). Additional significant and distinct market segments accounted for the following revenues in [REDACTED]: neuropathic pain \$ [REDACTED], migraine \$ [REDACTED] and fibromyalgia \$ [REDACTED].

The pain market is dominated by two major classes of drugs. Opioids and NSAIDs accounted for [REDACTED]% of the market by value in 2011, local anesthetic formulations held a [REDACTED]% share, and certain antidepressants and anticonvulsants respectively accounted for [REDACTED]% and [REDACTED]% market shares. The migraine market is almost completely attributable to sales of a small number of triptans, while off-label use of various drugs account for much of the neuropathic pain and fibromyalgia segments.

The high value (\$ [REDACTED]) opioid segment is dominated by sales of oxycodone (\$ [REDACTED]) and hydrocodone (\$ [REDACTED]), with Purdue's OxyContin formulation of oxycodone the only major branded product ([REDACTED] sales of \$ [REDACTED]). Generic opioid formulations have steadily eroded the sales of other branded opioids. Branded formulations of five drugs (Pfizer's Celebrex and Advil, Astellas' Celecox, Novartis' and Endo's Voltaren, Hisamitsu's Mohrus Tape and Daiichi Sankyo's Loxonin) collectively accounted for [REDACTED]% of NSAID revenues, with the two celecoxib (Celebrex and Celecox) formulations producing revenues of \$ [REDACTED]. Both oral and topical NSAID formulations are widely used, with the latter, such as Mohrus Tape, being especially popular in the Japanese market. Acetaminophen usage is mostly of OTC products such as Tylenol, or in combination with opioids as in Vicodin.

The use of local anesthetic formulations is mostly confined to the treatment of acute pain, especially postoperative pain, and during surgical procedures. This market segment generated revenues of \$ [REDACTED] in [REDACTED], with generic formulations increasingly important, but remains dominated by AstraZeneca, with a [REDACTED]% market share. More recently topical formulations of some agents have become available for certain chronic pain conditions, with Endo's Lidoderm generating revenues of \$ [REDACTED] for use in treating postherpetic neuralgia.

Symptoms of pain often arise in depressed patients, and it has been observed that certain antidepressants are effective in attenuating such symptoms and/or neuropathic pain. The more effective agents are certain tricyclic antidepressants, those which are tertiary amines, and the SNRIs duloxetine, venlafaxine and milnacipran, while bupropion is only effective in the treatment of neuropathic pain. The only agents of this type approved for the treatment of any forms of pain are Eli Lilly's Cymbalta (duloxetine), for fibromyalgia and chronic musculoskeletal pain, while in the U.S., Forest's Savella (milnacipran) is only approved for the treatment of fibromyalgia and not depression. It is estimated that approximately [REDACTED]% of Cymbalta's \$ [REDACTED] sales were from its use in the treatment of pain and fibromyalgia, dwarfing Savella's [REDACTED] revenues of \$ [REDACTED].

Anticonvulsant drugs were originally developed for the treatment of epilepsy. However, several anticonvulsants have been found to be useful in the treatment of pain, especially neuropathic pain. Of the older anticonvulsants, topiramate, oxcarbazepine and carbamazepine are the best established as useful in treating pain. The most useful agent is Pfizer's Lyrica (pregabalin) which is approved for the treatment of several pain indications. The bulk of U.S. sales of Lyrica and one-third of the global sales of \$ [REDACTED] are estimated to be due to its use in treating pain disorders.

The U.S. has by far the most significant pain therapeutic market, both in value and in its usage of certain opioids in particular. The pain markets in Europe and Japan are of significant value, respectively \$ [REDACTED] and \$ [REDACTED].

but the combination of lower drug usage, lower prices and greater use of generics ensures that these markets are much smaller in value.

In 2012, the U.S. acute and chronic pain market produced revenues of \$ [REDACTED], with opioids (\$ [REDACTED]) and NSAIDs (\$ [REDACTED]) providing the dominant segments. The most extensively used opioid is hydrocodone with over half of the [REDACTED] opioid prescriptions written for combinations of hydrocodone and acetaminophen such as Vicodin. Both opioid and NSAID market segments are dominated by generic products with OxyContin (\$ [REDACTED]) and Celebrex (\$ [REDACTED]) as the dominant branded products in these respective segments. Local anesthetics, antidepressants and anticonvulsants account for the remainder of this market, with generics dominant in each case.

In Japan and especially in Europe, the pain market segments are dominated by generic products with a greater usage of NSAIDs and much lower usage of opioids than the U.S. In Europe, Celebrex sales were only \$ [REDACTED] while Grünenthal's tramadol-based formulations Zaldiar and Tramal produced revenues of \$ [REDACTED], with other branded products producing modest revenues. In Japan, opioids accounted for just [REDACTED]% of the market (\$ [REDACTED]), but there is a more extensive use of both oral and topical NSAIDs. The latter segment is dominated by Hisamitsu's Mohrus products, with collective sales of \$ [REDACTED] and Daiichi Sankyo's Loxonin (\$ [REDACTED]), while Astellas' Celecox (\$ [REDACTED]) is the leading oral NSAID.

Three discrete, but smaller, pain segments are those of neuropathic pain, fibromyalgia and migraine. In the U.S., the value of the neuropathic pain segment was \$ [REDACTED] in [REDACTED], which was dominated by sales of Pfizer's Lyrica (\$ [REDACTED]) and Endo's Lidoderm (\$ [REDACTED]). Use of Eli Lilly's Cymbalta and generic gabapentin accounted for \$ [REDACTED] revenues. Lyrica (\$ [REDACTED]) is the dominant product in the European market, worth \$ [REDACTED] in [REDACTED], while Cymbalta is only approved to treat diabetic peripheral neuropathy. Lyrica, with sales of \$ [REDACTED], also dominates the \$ [REDACTED] Japanese market segment with Cymbalta not approved until February [REDACTED].