Opioids Market to 2018

Increasing Concentration of Abuse-Resistant Branded Generics Alter Competitive Dynamics in this Flat Market

GBI Research
Global Business Intelligence

GBI Research Report Guidance

- The report includes an executive summary, which provides an overview of the key points.
- Chapter three provides an overview of a selected group of the currently marketed opioid products.
- Chapter four includes a pipeline analysis of the opioid products currently in development, an overview of the developmental pipeline by phase and route of administration, as well as a summary of the promising pipeline products.
- Chapter five provides an overview of the Mergers and Acquisitions (M&As), licensing agreements, and co-development agreements in the opioids market since 2005. It also includes an analysis of each type of deal by year, geography, and value.

Executive Summary

Strong Diversification of Opioid Products across Pain Markets

Currently, XX opioid-based products are approved for a range of painful conditions across the seven major developed markets

The current opioids market is characterized by a very broad and highly diversified product portfolio. Patients experiencing moderate to severe pain caused by a range of underlying physiological conditions are treated almost exclusively with opioid analgesics. As a result, the therapeutic landscape across most pain markets for patient populations experiencing considerable levels of pain, with the exception of indications such as migraines, are heavily dominated by opioids. As a therapeutic drug class, opioids have virtually no competition from molecules with non-opioid receptor targets, although the current environment within this therapeutic class is highly competitive. Currently, XX opioid-based products are approved for a range of painful conditions across the seven major developed markets considered in this report, including the US, Germany, the UK, France, Italy, Spain, and Japan. These products are based on XX different opioid compounds and are differentiated according to a range of characteristics, including dosage, route of administration, and pharmacokinetic features, as well as increasingly on the basis of tamper-resistant formulation technologies.

Continual Trend towards Abuse-Resistant Formulations

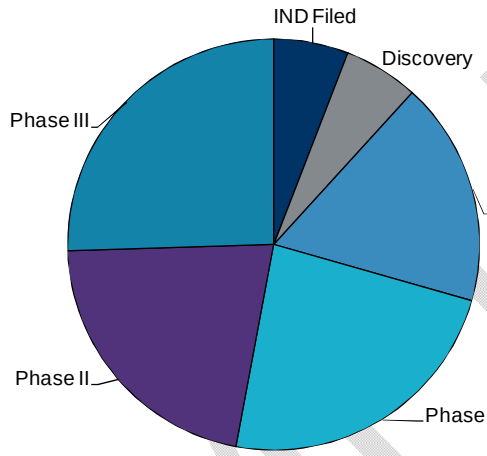
Due to growing concerns among regulatory authorities and physicians regarding increasing opioid abuse, particularly in the US, there has been a seismic shift towards developing abuse-resistant formulations of Extended-Release (ER) opioid analgesics. Since the 2009 US launch of Embeda (morphine sulfate and naltrexone hydrochloride), the first opioid product designed to be abuse-resistant, a whole range of novel products and reformulations of existing products have been brought to the market. Although abuse-resistant formulations do not confer any clinical benefits, they have nevertheless become an essential feature in the current market environment in order for products to remain competitive in the future. Due to growing regulatory requirements for opioid compounds, virtually every opioid-based, ER product that has been launched over the last three years has had to fulfill post-marketing study requirements in order to determine how effective these formulations are in deterring abuse. As these studies are designed to run for three years, there is currently little evidence available, and the evidence that has been obtained so far is inconclusive. However, the post-marketing data for Embeda have suggested that its safety profile is comparable to the standard ER morphine formulation, but may confer some degree of abuse resistance. While additional post-marketing data will be needed before a judgment about the effects of abuse-resistant formulation technologies can be made, the post-marketing data for Embeda can be considered as a positive beginning in the effort to curb opioid abuse. It is also important to note that the currently marketed products use different abuse-resistant formulation technologies, so the combined total effect of this novel generation of products on opioid abuse is currently unclear. However, identifiable trends are likely to become apparent over the next two years as more data from post-marketing studies become available.

The opioid R&D product pipeline is weak comprising only XX molecules including monotherapies and combination therapies

Weak Developmental Pipeline

The current developmental pipeline of opioid products for the management of a range of painful conditions is very small compared to the total revenue and patient pool for the existing products. This is indicative of a very low level of innovation and a high level of market saturation. GBI Research has identified a total of XX monotherapies and combination opioid-based therapies that are currently being tested for the treatment of acute and chronic pain, as well as for osteoarthritic, neuropathic, and post-operative pain. Three monotherapies and nine combination therapies are currently in the discovery or preclinical stages of development, respectively, while Investigational New Drug (IND) applications have been submitted for two developmental programs. Across the clinical stages of drug development, XX, XX, and XX monotherapies or combination therapies are currently in Phase XX, XX, and XX, respectively. Another three products have been filed for regulatory approval.

Opioids Market, Global, R&D Pipeline by Phase (%), 2012



Source: GBI Research's Proprietary Pipeline Products Database [Accessed Nov 8, 2012]

Note: NDA filed molecules not included

The opioids pipeline contains virtually no novel compounds in the later stages of development, which is indicative of a high level of competition and market saturation. The current late-stage products are differentiated on the basis of small and incremental changes in formulation, delivery, and speed of onset of analgesia, and also very frequently on the basis of the tamper-resistance of strong opioid compounds. Notably, no weak opioids are currently in development, which is strongly indicative of a perceived lack of incentives to develop products for patient populations suffering from moderate pain levels.

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2 Introduction

2.1 Introduction

2.1.1 High Levels of Product Diversification in a Highly Competitive Market Environment

The current opioids market is characterized by a very broad and highly diversified product portfolio. Patients experiencing moderate to severe pain caused by a range of underlying physiological conditions are treated almost exclusively with opioid analgesics. As a result, most patient populations are experiencing more severe levels of pain across most pain markets heavily dominated by opioids, with the exception of indications such as migraines. As a therapeutic drug class, opioids have virtually no competition from molecules with non-opioid receptor targets, although the current environment within this therapeutic class is highly competitive. Currently, XX opioid-based products are approved for a range of painful conditions across the seven major developed markets considered in this report, including the US, Germany, the UK, France, Italy, Spain, and Japan. These drugs are based on XX different opioid compounds and are differentiated according to a range of therapeutic characteristics, including dosage, route of administration, and pharmacokinetic features, as well as increasingly on the basis of tamper-resistant formulation technologies.

The World Health Organization (WHO) pain ladder provides broad guidelines for the treatment of pain and suggests that all pain should be treated. Pharmacological alleviation for mild to moderate pain levels initially includes non-opioid analgesics, such cyclooxygenase inhibitors or Non-Steroidal Anti-Inflammatory Drugs (NSAIDs). If this is unsuccessful, immediate-release mild opioids, such as codeine or tramadol, should be prescribed. If this still does not provide sufficient alleviation of pain, strong opioids can be administered. Morphine is generally considered effective in alleviating pain, although there are concerns associated with the long-term use of such strong opioids over months or even years. Alternatives to morphine include immediate-release hydromorphone and oxycodone (Jost and Roila, 2010).

2.1.2 Inconsistent Clinician Prescribing Preferences

Analysis of the prescription trends for opioids in the European markets in the recent past clearly indicates that the historically most widely prescribed opioids — namely, morphine, buprenorphine, oxycodone and fentanyl — remain the predominantly prescribed drugs, constituting more than XX% of all dispensed prescriptions for opioids in these markets. However, a survey among physicians in the UK indicates there is a lack of consistency and a considerable degree of variability in the preferences for any one of the leading opioids in this market in identical or closely-aligned patient populations. This variability indicates that inconsistent product perceptions drive prescribing preferences among physicians. This is likely due to the large fragmentation and diversification of the market based on active pharmaceutical ingredient, pharmacokinetic characteristics, drug-release properties, route of administration, as well as tamper- and abuse-resistance. Both the variability and inconsistency in physician prescribing preferences suggest that on a macroscopic level, novel products can displace the currently marketed and strongly-performing products, provided that they offer significant perceived benefits. These benefits are based primarily on efficacy, pharmacokinetic release properties, and the concomitant durability of pain relief and abuse- and tamper-resistance properties — with a smaller potential for differentiation based on safety and side effect profiles.

In the recent past, an entire range of companies have been competing in the area of opioid abuse-resistance, either by introducing novel products or re-formulating existing products, in order to remain competitive. From an overall historic perspective over the last two decades, the primary feature for differentiation in this competitive market has been the development of Extended-Release (ER) oral formulations, which provide very significant analgesic and pharmacokinetic benefits, but are also more prone to abuse due to their high dosages. These ER formulations also remain significantly higher priced than the immediate-release oral formulations and target significantly larger patient populations, thereby offering the greatest commercial potential due to higher profitability and potential for differentiation. While a considerable level of saturation has been reached in this market segment, there is a strong current trend towards abuse-resistant formulations, which do not provide any clinical benefits, but rather represent an attempt to address increasing concerns among both regulatory bodies and physicians regarding a growing opioid abuse epidemic. Since the launch of the first abuse-resistant ER opioid formulation, Embeda, in 2009 in the US, a very significant market shift has occurred in that either a range of new abuse-resistant products have been launched, or strongly-performing opioid products, such as Oxycontin (oxycodone), have been modified and now feature some forms of abuse-resistance.

4 Pipeline Analysis

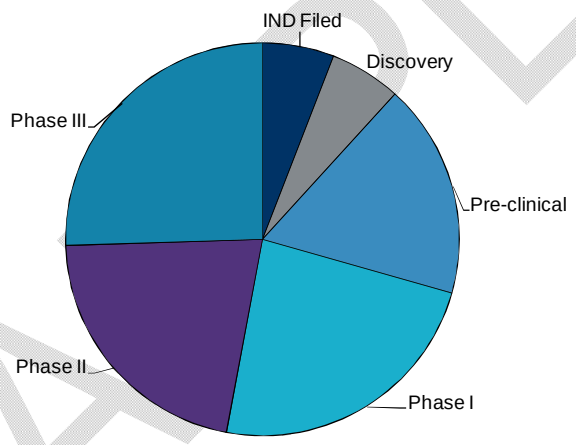
4.1 Introduction

The opioids pipeline contains virtually no novel compounds in the later stages of development, which is indicative of a high level of competition and market saturation

The current developmental pipeline of opioid products for the management of a range of painful conditions is very small compared to the total revenue and patient pool for the existing products. This is indicative of a very low level of innovation and a high level of market saturation. GBI Research has identified a total of XX monotherapies and combination opioid-based therapies that are currently being tested for the treatment of acute and chronic pain, as well as for osteoarthritic, neuropathic, and post-operative pain. Three monotherapies and nine combination therapies are currently in the discovery or preclinical stages of development, respectively, while Investigational New Drug (IND) applications have been submitted for three developmental programs. Across the clinical stages of drug development, XX, XX, and XX monotherapies or combination therapies are currently in Phase XX, XX, and XX, respectively. Another three products have been filed for regulatory approval.

The opioids pipeline contains virtually no novel compounds in the later stages of development, which is indicative of a high level of competition and market saturation. The current late-stage products are differentiated on the basis of small and incremental changes in formulation, delivery, and speed of onset of analgesia, and also very frequently on the basis of the tamper-resistance of strong opioid compounds. Notably, no weak opioids are currently in development, which is strongly indicative of a perceived lack of incentives to develop products for patient populations suffering from moderate pain levels.

Figure 2: Opioids Market, Global, R&D Pipeline by Phase (%), 2012



Source: GBI Research's Proprietary Pipeline Products Database [Accessed Nov 8, 2012]

Note: NDA filed molecules not included

5 Deals Analysis

5.1 Overview:

This section provides an overview of the M&As, and licensing and co-development agreements across multiple pain indications in which opioids are frequently used in patients suffering from moderate to severe pain. Indications considered in this context include chronic and acute pain, as well as neuropathic, osteoarthritic and post-operative pain. The section also includes deals involving companies and compounds that are not in direct competition with opioid products, and provides a general overview of the recent consolidation landscape in the pain market.

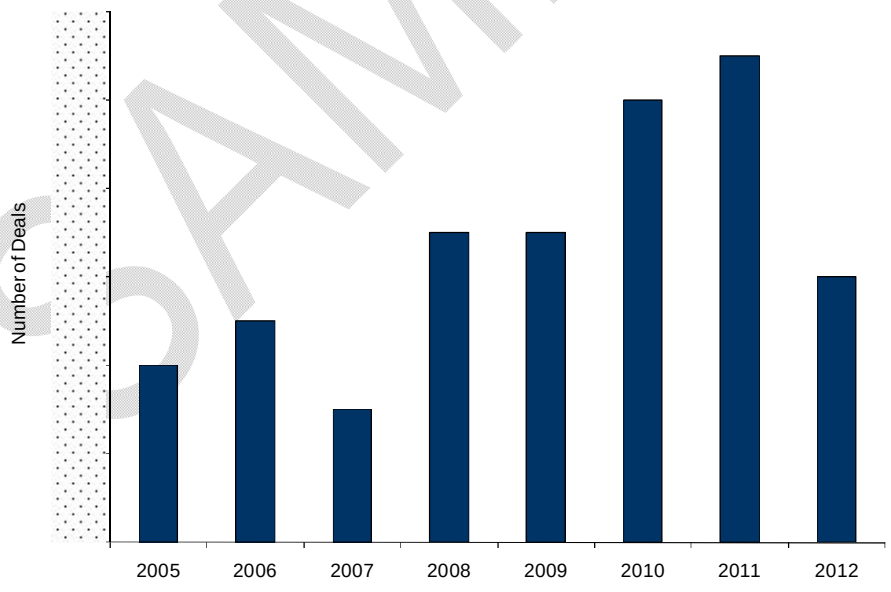
5.1.1 M&As by Year

Since 2005, XX M&As have been identified across the pain indications

Since 2005, 53 M&As have been identified across the pain indications noted above. The combined total value of these deals where disclosed amounts to just over $XX billion, indicating a very robust trend towards consolidation. Annual counts of M&As in the opioids market indicate that the number of these deals has grown steadily between 2005 and 2012, as shown in Figure 9. However, the number of M&As was exceptionally low in 2007 and did not confirm the overall trend. The primary underlying reasons for this trend are increasingly uncertain pain markets with a large array of product portfolios across several indications that are largely dominated by generics or branded generics.

Despite these dynamic changes and the resulting pricing pressure, the concentration and dominance of these markets by a relatively small number of products have resulted in a growing degree of uncertainty and risk in developing new products and in remaining competitive through innovations in existing product lines. Nonetheless, the pain markets across these indications remain highly lucrative from a commercial standpoint due to substantial and growing patient populations and, in the case of opioids, comparatively low production costs as well as comparatively low risks and high success rates for novel products that are based on established and generic opioid compounds. However, commercial success in these markets depends very strongly on the extent and qualitative benefits of these products based on differentiation and price.

Figure 9: Opioids Market, M&As by Year, 2005–2012



Source: GBI Research's Proprietary Pipeline Products Database [Accessed Nov 20, 2012]

Note: Only M&As reported within the first five months of 2012 are included.

6 Appendix

6.1 Abbreviations

Anti-NGF: Anti-Nerve Growth Factor

API: Active Pharmaceutical Ingredient

BDSI: BioDelivery Sciences International

BEMA: BioErodible MucoAdhesive

BMS: Bristol-Myers Squibb

CNS: Central Nervous System

CO_2: Carbon Dioxide

CR: Controlled Release

DSP: Dainippon Sumitomo Pharma

EMA: European Medicines Agency

ER: Extended Release

FDA: Food and Drug Administration

FIC: First-in-Class

GSK: GlaxoSmithKline

IND: Investigational New Drug

KHK: Kyowa Hakko Kirin

m: million

M&As: Mergers and Acquisitions

MOA: Mechanism of Action

MPI: Myriad Pharmaceuticals, Inc.

NASDAQ: National Association of Securities Dealers Automated Quotation

NDA: New Drug Application

NMDA: N-Methyl-D-Aspartate

NRI: Norepinephrine Reuptake Inhibitor

NSAID: Non-Steroidal Anti-Inflammatory Drug

NX: Naloxone

NYSE: New York Stock Exchange

OMJPI: Ortho-McNeil-Janssen Pharmaceuticals

ORL1: Opioid Receptor-Like1

PCA: Patient-Controlled Analgesia

R&D: Research and Development

REMS: Risk Evaluation and Mitigation Strategy

RLS: Restless Legs Syndrome

SRI: Serotinin Reuptake Inhibitor

TRPV1: Transient Receptor Potential Vanilloid sub-family 1

TRPV3: Transient Receptor Potential Vanilloid sub-family 3

WHO: World Health Organization

6.2 Bibliography

Davis MP (2010). Opioid receptor targeting ligands for pain management: a review and update. *Expert Opinion on Drug Discovery*; 5(10): 1007-1022.

U.S. Department of Health and Human Services (2011) Drug Abuse Warning Network, 2009: National Estimates of Drug-Related Emergency Department Visits

Badalamenti VC, Buckley JW, Smith ET (2012) Safety of EMBEda (morphine sulfate and naltrexone hydrochloride) extended-release capsules: review of postmarketing adverse events during the first year, *Journal of Opioid Management*, 8,115-25

6.3 Research Methodology

GBI Research's dedicated research and analysis teams consist of experienced professionals with marketing, market research, and consulting backgrounds in the pharmaceutical and medical devices industry, as well as advanced statistical expertise.

GBI Research adheres to the codes of practice of the Market Research Society (www.mrs.org.uk) and the Society of Competitive Intelligence Professionals (www.scip.org).

All GBI Research databases are continuously updated and revised.

6.3.1 Coverage

The objective of updating GBI Research coverage is to ensure that it represents the most up-to- date vision of the industry possible.

Changes to the industry taxonomy are built on the basis of extensive research of company, association, and competitor sources.

Company coverage is based on three key factors: market capitalization, revenues, and media attention/innovation/ market potential.

- An exhaustive search of 56 member exchanges is conducted and companies are prioritized on the basis of their market capitalization;
- The estimated revenues of all major companies, including private and governmental, are gathered and used to prioritize coverage; and
- Companies that are making the news, or that are of particular interest due to their innovative approach, are prioritized.

GBI Research aims to cover all major news events and deals in the medical industry, updated on a daily basis.

The coverage is further streamlined and strengthened with additional inputs from a GBI Research Expert Panel (see below).

6.3.2 Secondary Research

The research process begins with exhaustive secondary research on internal and external sources being carried out to source qualitative and quantitative information relating to each market.

The secondary research sources that are typically referred to include, but are not limited to:

- Company websites, annual reports, financial reports, broker reports, investor presentations, and SEC filings.
- Industry trade journals, scientific journals, and other technical literature;
- Internal and external proprietary databases;
- Relevant patent and regulatory databases;
- National government documents, statistical databases, and market reports;
- Procedure registries; and
- News articles, press releases, and web-casts specific to the companies operating in the market.

6.3.3 Primary Research

GBI Research conducts hundreds of primary interviews a year with industry participants and commentators in order to validate its data and analysis. A typical research interview fulfills the following functions:

- It provides first-hand information on the market size, market trends, growth trends, competitive landscape, and future outlook;
- It helps in validating and strengthening the secondary research findings; and
- It further develops the analysis team's expertise and market understanding.

Primary research involves email interactions and telephone interviews, as well as face-to-face interviews for each market, category, segment, and sub-segment across geographies.

The participants who typically take part in such a process include, but are not limited to:

- Industry participants: CEOs, VPs, marketing/product managers, market intelligence managers, and national sales managers;
- Hospital stores, laboratories, pharmacies, distributors, and paramedics;
- Outside experts: investment bankers, valuation experts, and research analysts specializing in specific medical equipment markets;
- Key Opinion Leaders (KOLs): physicians and surgeons specializing in different therapeutic areas corresponding to different kinds of medical equipment.

6.3.4 Pipeline Analysis

This section provides a list of molecules at various stages in the pipeline for various indications. The list is sourced from an internal database and is validated for the accuracy of phase and mechanism of action at ClinicalTrials.gov and company websites. The section also includes a list of promising molecules that is narrowed down based on the results of the clinical trials at various stages and the novelty of the mechanism of action.

6.3.5 Expert Panel Validation

GBI Research uses a panel of experts to cross-verify its databases and forecasts.

GBI Research's expert panel comprises marketing managers, product specialists, international sales managers from medical device companies, academics from research universities, KOLs from hospitals, consultants from venture capital funds, and distributors/suppliers of medical equipment and supplies.

Historic data and forecasts are relayed to GBI Research's Expert Panel for feedback and adjusted in accordance with their feedback.

6.5 Disclaimer