

Opportunities in Gastroenterology

Despite being one of the world's largest therapeutic areas and presenting huge burdens to healthcare and economies globally, many of the diseases of the gastrointestinal (GI) tract are not well understood and less than optimally treated. This article discusses that, given the large public need and the propensity for high returns, the gastroenterology market represents potentially fruitful hunting grounds for companies both large and small.

Gastrointestinal (GI) disorders are among the most common types of complaints made to primary care physicians worldwide and are associated with substantial healthcare and economic burden¹. Each year, more than 100 million people are diagnosed with a GI disorder, resulting in 200 million sick days, 50 million medical visits, 16.9 million days lost from school, 10 million hospitalisations and nearly 200,000 deaths per year². In 2005, in the US alone, GI disorders cost the payers and the government nearly \$110 billion in direct healthcare expenditures². In recent years, GI prescriptions have remained one of the world's largest therapeutic markets, with sales of more than \$20 billion and single digit growth³.

Despite the significant healthcare and economic burden of GI disorders worldwide, many digestive diseases are still poorly understood and treatment options are far from optimal, leaving many patients dissatisfied with their current treatment. Thus, from a volume/value perspective, the significant area of unmet need and room for further development, combined with the large share of the pharmaceutical market, make the GI sector an attractive target for therapeutic development, where the development of new, innovative and more cost-effective treatments could result in greater patient satisfaction, reduced economic burden and higher-profit returns².

Market segmentation

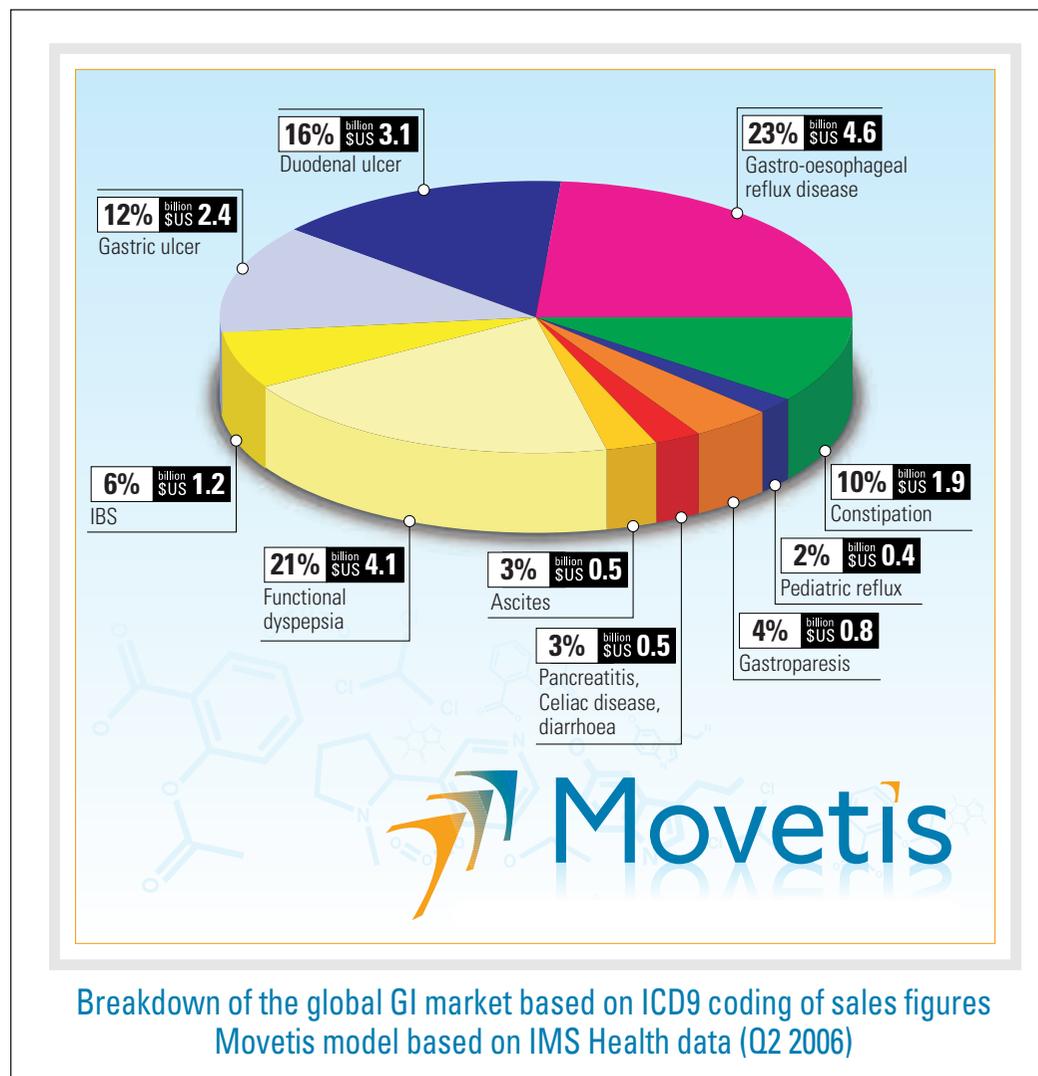
The definition of the GI market varies between authors. For the sake of this article we have defined the GI market by disease areas consisting of a series of disorders that are the result of impaired functioning of propulsion and movement in the GI tract, disturbed secretion in the GI system or impaired functioning of specific GI organs that are not the result of an inflammation. Therefore, larger market segments such as IBD and Hep C will not be discussed. Furthermore, these segments have changed so dramatically in recent years that they would merit a separate discussion.

At present, one of the largest sub-segments of the GI market is dominated by drugs that regulate acid secretion in patients with peptic ulcer, duodenal ulcer and gastro-oesophageal reflux disease (GORD), also commonly known as acid reflux (see **Figure 1**). In patients with GORD, one of the largest and growing GI segments, liquid content of the stomach regurgitates back up into the oesophagus causing ulcerations of the oesophagus, the predominant symptom of which is the unpleasant sensation of heartburn, especially at night. Acid suppressants used in the treatment of GORD include proton pump inhibitors, histamine H₂ receptor antagonists as well as antacids; however, proton pump inhibitors (PPI) have emerged as the most effective treatment option. PPI work by reducing the amount of gastric acid produced in

By Dirk Reyn

Therapeutics

Figure 1
Market share of
GI sub-sectors



the stomach, thereby limiting the amount of gastric acid that can regurgitate into the oesophagus and cause damage. One such proton pump inhibitor is the blockbuster drug NEXIUM® (esomeprazole), which in 2005 alone was associated with sales revenues of more than \$4 billion² and in 2006 more than \$6 billion³. Due to the excellent efficacy of currently available PPI, which are effective in 85-90% of patients, and the availability of a high number of generic H₂ antagonists and PPIs, it has become difficult to bring a newer, more cost-effective agent to the market that provides a significant clinical benefit over current standard of care². However, even within this well established market, there is potential for further development. Up to 10% of patients with GORD, approximately five million, continue to complain of persistent nocturnal heartburn and severe dyspeptic symptoms – chronic or recurrent pain or discomfort centred in

the upper abdomen – and severe bloating and may benefit from another type of treatment. In these patients, underlying motility problems such as increased frequency of relaxation of the sphincter between the stomach and the oesophagus, delayed emptying of the stomach and impaired oesophageal motility, rather than increased acid secretion, have been suggested as important contributing factors. Children with GORD have a less typical acid reflux requiring interventions that prevent food or bile from being regurgitated.

The second most important segment includes functional GI diseases such as irritable bowel syndrome (IBS) and dyspepsia. Despite the high prevalence of these functional disorders, existing therapies are associated with suboptimal efficacy. Several well controlled studies have failed to provide consistent evidence for the use of acid suppression in these disorders. Also, other drugs like

spasmolytics or first generation promotility drugs have not been able to provide consistent results in large trials or have a less acceptable benefit/risk ratio. Recent research has suggested that the heterogeneous efficacy results are probably caused by the variety of underlying pathologies in these disorders; including impaired gastric motility, gastric hypersensitivity, gastric dysaccomodation, increased levels of certain GI dominant neurotransmitter and gastric inflammation.

Although supported by a much stronger set of efficacy data, a number of older promotility compounds have been associated with an unfavourable safety profile. For example, Primperan™ (metoclopramide) is associated with rare but serious dopamine-mediated neurological side-effects. PREPULSID® (cisapride), which was previously recommended as the drug of first choice for abnormal upper GI motility disorders, is no longer widely available. Due to its lack of specificity for the 5-HT₄ receptor, the drug was associated in 2001 with very rare cardiovascular events in patients with pre-existing cardiac disease and/or in combination with a list of CYP3A4 metabolised drugs. Similarly, the two drugs that have been approved in the US for the treatment of IBS now have restricted use because of potential safety concerns. ZELNORM® (tegaserod) – another non-specific serotonin 5-HT₄ receptor agonist that impacts other physiological processes – is restricted for use in women younger than 55 years of age with constipation-predominant IBS or chronic constipation (CC). The same agent, marketed as ZELMAC®, failed to gain approval in the European market where authorities were concerned about the marginal benefits seen in large IBS clinical trials compared with placebo². LOTRONEX (alosetron), another FDA-approved agent for IBS, is limited to use in women with severe diarrhoea-predominant IBS due to severe forms of diarrhoea and colitis.

The remaining segment(s) consists of diseases such as diarrhoea or constipation where the underlying mechanisms of diseases are more straightforward and where older and cheaper drugs have provided relief for a large group of patients or diseases like ascites and pancreatitis where no effective treatment exists. Although little dedicated research has been performed in these conditions in the past 10 years, analysts predict that this sector is about to grow. Some of the reasons for this include changing demographics, a shift in eating habits to a more Western diet, restriction in fibre-intake, increase in alcohol usage, increased incidence of Hep C as underlying cause of a number of GI conditions, more poly-medicated elderly with specific

Need help in understanding the market for new screening technologies?



HTStec is an independent market research consultancy, focused on providing informed opinion and market research on the technologies that underpin drug screening today. HTStec offers companies that are developing novel liquid handling, detection instruments, laboratory automation, assay reagents and platform technologies a range of consulting services and published market reports.

To find out how HTStec can help you maximize the market potential of your developments visit...

www.htstec.com



Therapeutics

GI disorders and widespread distribution of parasitic diseases. As a result, larger groups of patients will need newer, more effective treatments for GI disorders currently considered as areas of lower unmet need.

Areas of unmet need and therapeutic opportunities in GI

Despite the significant burden that these GI disorders have on healthcare systems, research into the underlying causes of GI disorders has been slow and less funded in most areas⁴. Perhaps, in part, due to the fact that they are often not considered life threatening, perhaps due to a lack of awareness of the magnitude and impact these disorders have on health economics and patient quality of life.

Also, the probability of finding a next NEXI-UM-size blockbuster drug in the GI area has become smaller, and this has negatively influenced the priority of GI drugs in portfolio analysis of major pharma players. Interestingly however, this is opening up the market to an increasing number of small- and medium-sized speciality companies able to generate a new spur of innovation in this area and are filling up the void left by big pharma.

It is clear that there remains a significant area of unmet need in the GI sector and that elucidation of the underlying causes of these diseases is of the utmost importance. Indeed, as new research now delves into the GI arena, light is being shed on the pathophysiology of these diseases, creating new opportunities for drug development – both in terms of new drug targets, and in terms of how to further enhance existing therapies. For example, the identification of a new class of compounds – aquaretics – may lead to a reduction in mortality rates in patients with ascites, while the refinement and development of very selective 5-HT₄ agonists may lead to agents with improved efficacy and safety profiles for the treatment of lower bowel motility disorders such as CC or IBS. Although there may be less room for the development of low price first-line agents in areas such as acid regulation, there are various areas within the GI sector where there is still an opportunity to develop treatments that will significantly improve the lives of potentially millions of patients worldwide. There is still great potential to create large value for patients, companies and investors in both low- and high-volume markets within the GI sector through development of leading therapies in areas such as CC, paediatric reflux, specific sub-segments of IBS, diabetic gastroparesis, pancreatitis, secretory diarrhoea and ascites, where current therapies are far from ideal.

Specific areas of drug development that currently look promising include research into highly selective serotonin 5-HT₄ agonists, ghrelin agonists, vasopressin V2 receptor antagonists, 5-HT₄ antagonists and cyclic guanosine monophosphate-dependent protein kinase (cGMPII) antagonists.

High affinity serotonin 5-HT₄ agonists, have the potential to treat abnormalities in gastrointestinal motility by offering a higher efficacy and better benefit/risk ratio when compared to current treatment options which are often associated with sub-optimal efficacy, adverse side-effects and inconvenient dosing regimens.

Vasopressin V2 receptor antagonists, also known as aquaretics, offer a novel approach to treating liver disorders resulting in fluid/water retention such as ascites. They work by reducing renal water resorption which leads to increased water excretion and increased urinary output. Vasopressin V2 receptor antagonists, like diuretics, reduce fluid retention, but unlike diuretics, are not associated with significant electrolyte loss, thus placing patients at lower risk of the severe clinical consequences of an inappropriate electrolyte balance (eg hyponatraemia).

Another group of novel agents, 5-HT₄ antagonists, may reduce overexpression of serotonin in patients with celiac disease, IBS and certain GI cancers.

New drug targets are being identified through better understanding of disease pathways. For example, recent advances in the understanding of diarrhoeal disorders have shown that, in many cases, enterotoxins produced by the widely present bacterium in our bowels *Escherichia coli* activate a cGMP-mediated internal cascade that leads to increased chloride, and subsequently water secretion into the gut lumen. The clinical consequence of this is various diarrhoeal disorders, including traveller's diarrhoea, diarrhoea-predominant IBS, as well as other forms of diarrhoea, which is considered to be a major cause of infant mortality. Elucidation of this pathway in the pathology of diarrhoea is helping to pave the way for development of potential new therapies⁵. For example, new agents are now being developed that specifically block the activation of this internal cascade, thereby preventing diarrhoea – highlighting just how important it is that we continue to research disease aetiology and pathology.

Detailed example of chronic constipation

At present, more than 80 million people worldwide, approximately 24 million of whom live in

Therapeutics

References

- 1 Bodger, K, Daly, MJ, Heatley, RV, Williams, DR. Clinical economics review: gastroenterology. *Aliment Pharmacol Ther* 1996;10:55-60.
- 2 IMS Health. IMS Health report. In: IMS Health.
- 3 Visiongain. The World Gastrointestinal Disorders Market 2006-2011. In: 2006.
- 4 Mayer, EA, Bradesi, S, Chang, L, Spiegel, BM, Bueller, JA, Naliboff, BD. Functional GI disorders: From animal models to drug development. *Gut* 2007.
- 5 Thapar, N, Sanderson, IR. Diarrhoea in children: an interface between developing and developed countries. *Lancet* 2004;363:641-53.
- 6 Miller, V, Hopkins, L, Whorwell, PJ. Suicidal ideation in patients with irritable bowel syndrome. *Clin Gastroenterol Hepatol* 2004;2:1064-8.

Europe, suffer from constipation of different origin². The prevalence of these disorders rivals that of asthma, depression and hypertension. Of these patients, approximately six million in Europe receive a prescription for acute or chronic treatment, making the total prescription market size comparable to that of asthma². CC is associated with a significant burden on healthcare resources. In particular, CC is associated with a high utilisation of specialist resources. It is estimated that 50-60% of prescriptions for more severe CC are written by specialists, while GPs mostly do the follow-up as patients run out of options after having tried several laxatives².

Despite the high demand, data show indeed that current treatments for CC are suboptimal, with 25% of those patients who receive a prescription (more than two million patients) being unsatisfied or not having a satisfactory response to treatment and having to continuously look for alternatives².

Currently, the total worldwide constipation market is valued at \$2 billion and is dominated by older, cheap treatments, including osmotic, bulk and stimulant laxatives.

It is clear that this large market of unsatisfied CC patients still represents a significant unmet need and commercial opportunity. RESOLOR® (prucalopride) is currently the first drug in a new subclass of targeted (more pronounced effect on bowel motility), specific and high-affinity 5-HT₄ agonists/motility drugs (called 'enterokinetics') with potential for safe treatment of CC. RESOLOR specifically treats the underlying motility problem and this new generation compound has shown consistent efficacy and safety profiles in three very large clinical trials to date. Unlike old generation 5-HT₄ agonists, the new generation of compounds have demonstrated that they have a more focused effect and are free of non-target related side-effects. So far, RESOLOR has been studied in 83 trials including six phase III trials involving more than 2,000 subjects and has demonstrated robust improvements in symptoms and quality of life data. It is as a once-daily regimen, which simplifies treatment compared with a complex schedule of laxatives that many patients have come to rely on.

Bringing these agents to market could lead to significant benefits for patients and reduce the burden on healthcare systems in terms of reduced doctor visits, hospitalisations and patient morbidity.

Creating value in the GI market

Various areas exist where it is possible to create greater value in the GI market. Steps need to be

taken to better educate healthcare professionals and the general public of the impact that a number of GI disorders have on patient quality of life and the burden that they have on healthcare systems. Indeed, recent data challenge the commonly held view that all GI disorders are 'lifestyle' conditions that do not merit pharmaceutical treatment or innovation. IBS, for example, which is commonly considered to be more of a 'nuisance' than a disease that can have serious consequences, has been associated with hopelessness because of symptom severity, interference with life, and a high rate of suicide ideation⁶.

There is also a need for establishing strategic partnerships in research and development to bring innovation back into the GI market. This includes researching the causes of disease and expanding the current knowledge base of disease pathology, as well as developing new agents that offer better efficacy, improved safety profiles, and/or less complex dosing at a price that is cost-effective compared with current therapy. In addition to this, it is also important that diagnostic and treatment guidelines are constantly refined, as it is important to ensure that data is properly understood and that medicines are used appropriately.

Conclusion

Given the large public need and the propensity for high returns, the gastroenterology market is set to expand. As an increasing pool of smaller speciality pharmaceutical players recognise the need and importance of developing innovative treatments to restore normal function of the GI system and improve patients' quality of life, the doors to improved GI health are opening, and opportunity calls. **DDW**

Dirk Reyn, MBA, Pharm, current CEO of Movetis Pharmaceuticals, was head of the GI Strategic Marketing Group for many years and then Vice President New Business Development for Janssen-Cilag in Europe. Dirk has more than 25 years of experience – he first joined J&J in 1992 and became the driving force behind the global marketing and commercial strategy for such products as PREPULSID® and PARIET® and other compounds from the GI portfolio.