Breathing Easier
The US Market for Asthma Therapies

Executive Summary

Asthma is a disease involving chronic inflammation and hyperresponsiveness of the airways. It is characterised by attacks of breathlessness and "wheezing" that sometimes result in death. Although asthma is known to be an inherited disorder that is triggered by environmental factors (allergens), the genetic basis for susceptibility to the disease remains unclear. Approximately 19 million people in the US have asthma, and the condition is responsible for over 5,500 deaths per year. Alarmingly, the number of people with asthma has recently been increasing at about 5% per year in the US and the mortality rate has increased as well. Asthma is a complex biologic process that is not completely understood; however, a consensus has emerged that asthma symptoms are manifestations of an allergic response driven by the immune system and linked to an IgE antibody response. Asthma has traditionally been divided into two types: allergic asthma, characterized as reaction to known external allergens, and nonallergic atopic asthma, in which allergens have not been defined.

Development of new drugs for asthma therapy has been active in recent years and is expected to remain so over the next several years. In fact, there is more effort being put into developing novel therapeutics for asthma than for any other disease involving the respiratory system. Market sales have experienced single-digit growth in recent years but new product introductions are expected to stimulate growth in the coming years. Anti-inflammatory technologies had the single largest block of dollar sales in 2001, accounting for 70% of the total market for asthma therapy drugs. Anti-inflammatories will continue to be the dominant technology through to 2006 and will not lose much ground to other technologies. Corticosteroid products had the largest sales in the anti-inflammatory technology group in 2001, accounting for 40% of total volume. Corticosteroids will maintain their position in 2006, but will lose some market share to other technologies. Adis Business Intelligence expects that the combination adrenergic/corticosteroid products, which combine elements of the top two monotherapy formulations, will be the new drugs with the greatest market impact.

GlaxoSmithKline (GSK) holds the number one position with almost 40% of the volume in 2001, although Adis Business Intelligence expects GSK's share to decrease to 34% by 2006. However, not only is GSK expected to maintain the number one brand in both adrenergic and corticosteroid therapy, it is expected that it will quickly dominate the adrenergic/corticosteroid combination therapy as well. **AstraZeneca**, with sales that put the company in the number two position, stays even during this time frame. **Aventis** brands are not expected to do as well and company share will only increase slightly, from 5% in 2001 to 6% in 2006. GSK is committed to maintaining its leadership position, with a broad development program in place and five late-stage products, one of which will be introduced in 2002. GSK's efforts in the shortterm are focussed on proven high-level technologies – i.e. adrenergic agents and corticosteroids – and should be successful in keeping this company in the number one position in asthma therapy.

Aventis and **Schering-Plough** both have the most launch programs for new asthma therapy drugs through to 2006, closely followed by AstraZeneca and **Novartis**. However, none of Aventis' late-stage programs are breakthrough and its marketing effort is not expected to generate above-average performance; therefore, sales will probably grow only moderately. AstraZeneca and Novartis also have fairly active development programs. However, like Aventis, their late-stage products are not breakthrough so sales growth will depend on marketing effort.

Asthma is a disease involving chronic inflammation and hyperresponsiveness of the airways. It is characterised by attacks of breathlessness and "wheezing" that sometimes result in death. Although asthma is known to be an inherited disorder that is triggered by environmental factors, the genetic basis for susceptibility to the disease remains unclear. The three main clinical features of asthma are bronchoconstriction, mucus plug formation and inflammation. The role of inflammation in causing asthma has been recognized for the last decade. During this time there has been considerable effort to develop anti-inflammatory drugs for asthma treatment and several have recently been launched.

Approximately 19 million people in the US have asthma and the condition is responsible for over 5,500 deaths per year. Alarmingly, the number of people with asthma has recently been increasing at about 5% per year in the US and the mortality rate has increased as well. Between 1979 and 1995, the age-adjusted death rate increased 67% from 0.9 per 100,000 in 1979 to 1.5 in 1995, while the age-adjusted death rate from all causes declined 12.7%. In prevalence by age, asthma is more prevalent in childhood than in adulthood, and tends to decline slightly throughout the adult years. The prevalence rate versus that of the total population indexes at 123 for people under 18, declines to 92 in the 18–44 age range, then 91 in the

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45–64 range, and 90 in the >65 range. Asthma is more frequent in the black population, and the age-adjusted death rate for blacks from asthma is three times that of whites.

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The Physiology of Asthma

Asthma is an extremely complex biologic process and is not fully understood. The disease is initially triggered by allergens such as ragweed, pollen, house dust mites, cockroach debris and pet dander, as well as environmental pollutants and pollutants encountered in the workplace. On the first exposure only rare B- and T-lymphocytes can recognize the allergens and respond. However, repeated exposure to the allergens in a genetically susceptible individual results in proliferation of the allergen-specific lymphocytes and ultimately a rapid and acute response. When the T-lymphocytes recognize allergen, they secrete cytokines (interleukins, interferons and growth factors) that stimulate other cells in their vicinity to secrete proinflammatory factors and chemoattractants and to up-regulate cell-adhesion molecules. In addition, the T cells stimulate allergen-specific B-lymphocytes to produce IgE antibodies. The inflammatory substances, in turn, are chemoattractants that feed back to amplify and modify harmful immune responses.

The identity of the allergens most responsible for triggering asthma has come to be better understood in recent years. General airborne outdoor air pollutants seem not to be the prime causes, because air quality has improved markedly in industrialized countries, while asthma rates have climbed. Yet asthma is associated with areas of economic development, as illustrated by a 1991 study in Zimbabwe. There, asthma affected only 0.1% of children living in rural villages, but 5.8% in a prosperous section of the capital Harare. It now seems that time spent in closed buildings and indoor allergens are crucial to development of asthma. In a 1997 study of asthmatic children from impoverished neighborhoods, led by Dr Rosenstreich of New York's Albert Einstein College of Medicine, cockroach allergies were found to be by far the leading cause.

Classification of asthma

Asthma has traditionally been divided into two types: allergic asthma, characterized as reaction to known external allergens, and nonallergic atopic asthma, in which allergens have not been defined. The onset of the allergic form usually occurs in childhood or in the young adult years. In general, epidemiological studies have indicated that perhaps one-third of children with asthma at puberty find that their asthma disappears in adulthood. Atopic asthma generally first appears in adulthood. The causes of asthmatic attacks in these individuals generally include:

- exercise/hyperventilation
- weather changes (cold air, heat and humidity)
- respiratory infections
- extreme emotional expressions (crying, anger or fear).

Nonetheless, the symptoms are still mediated primarily through IgE antibodies. Even when asthma has clinically disappeared, a patient's lung function is frequently altered, and the patient experiences continuing airway hyperresponsiveness with persistent coughing.

The central role of T-lymphocytes

Despite the division of asthma into allergic (IgE-dependent) and nonallergic categories, a consensus has emerged that all asthma symptoms are manifestations of an allergic response that is driven by the immune system and linked to an IgE antibody response. The usual immune reaction to invasion by foreign stimuli is the immediate activation of lymphocytes to generate cellular and humoral responses. In nonasthmatic subjects, these stimuli activate lymphocytes necessary for a specific immune response and then the response shuts down.

In asthma, antigens or allergens are processed and presented to T-helper (Th) lymphocytes by macrophages and B-lymphocytes via major histocompatibility complex (MHC) class II molecules. It is still unclear what influences the development of T-helper cells, but in the allergic response a specific subtype of T-lymphocyte, Th-2 helper cells, predominates over another subset, Th-1 helper cells. Activated Th-2 lymphocytes are the primary source of interleukin-4 (IL-4) and IL-5. These cytokines promote the switching of IgG and IgM synthesis by the B-lymphocyte to allergen-specific IgE synthesis. Once a tissue is sensitized by a specific allergen, exposure to the same allergen results in an augmented IgE response. Subsequently, activation of mediator cells – mast cells and

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eosinophils – plays a key role in the maintenance of this process. The accumulation of these activated leukocytes provokes an inflammatory response that damages epithelial cells.

The inflammation mediators also activate neurogenic mechanisms that cause bronchoconstriction and augment the vascular permeability, vascular leakage, edema (swelling) and mucus production characteristic of asthma. Ultimately, the inflammatory process combined with vascular leakage and edema result in hyperresponsiveness of airway smooth muscle and long-term cellular damage to the bronchial airways. Why the inflammatory response in asthmatics does not shut down is a mystery. Instead, "early" and "late" asthmatic responses are perpetuated in genetically predisposed individuals. In any event, the asthmatic process is now recognized as characterized by chronic inflammation and a recurrence of immunologic events.

Early-phase allergic asthma

Mast cells are resident in connective tissue below epithelial surfaces and certain other areas in the body. They synthesize and store inflammatory mediators, ready for a rapid assault on microbial pathogens. Upon stimulation by IgE antibodies, mast cells release a variety of proinflammatory substances, notably:

- Histamine, which causes bronchoconstriction and mucus secretion.
- Cytokines prominent in the progression of the inflammatory cascade such as IL-3, IL-4, IL-5 and IL-13. IL-4 promotes the proliferation and differentiation of the Th-2 subset of T-lymphocytes and augments the differentiation of B-lymphocytes to produce IgE antibody. Consequently, IL-4 has become a prime target for researchers. Also, investigators at Johns Hopkins University and at the University of California at San Francisco recently reported that blocking IL-13 can completely prevent asthma attacks in a mouse model. There is now a concerted effort to find drugs that will function as specific blockers of this cytokine. Other interleukins variously accelerate mast-cell proliferation (IL-3), activate eosinophils (IL-5), induce eosinophils to secrete other cytokines (IL-8) and induce expression of low-affinity IgE receptors. The growth factor granulocyte-macrophage colony-stimulating factor (GM-CSF) also activates eosinophils. Tumor necrosis factor α (TNFα), produced by pulmonary macrophages, is believed to act as a chemoattractant and to up-regulate specific cell-adhesion molecules. Whether TNFα also has direct proinflammatory effects has not been established. What is known is that the TNFα level is elevated in asthmatics who exhibit symptoms.
- Cell-adhesion molecules, which are up-regulated by the cytokines in the initial response. The adhesion properties of epithelial and endothelial cell are thereby increased. A number of specific adhesion molecules have been identified and have become the targets for potential therapeutic intervention. These include E-Selectin, ICAM-1 (intercellular adhesion molecule 1), VCAM-1 (vascular adhesion molecule 1) and VLA-4 (very late antigen 4). The adhesion of monocytes, granulocytes and, in particular, eosinophils to airway cells is crucial in increasing the local concentration of inflammatory mediators that cause hyperresponsiveness. The resulting damage to the airway epithelium and endothelium perpetuates the asthmatic process.
- Eicosanoids; i.e. leukotrienes, thromboxanes and prostaglandins. When IgE binds to its receptor on mast cells, phospholipase A2 is activated and arachidonic acid is released from the cell membrane. Leukotrienes and prostaglandins/thromboxanes are then generated as a result of oxidation of free arachidonic acid by the enzymes 5'-lipoxygenase and cyclooxygenase, respectively. The activation of related inflammatory cells, such as macrophages, monocytes, eosinophils and basophils, also leads to the production of eicosanoids. Leukotrienes promote chemotaxis (attraction of additional white blood cells to the area of inflammation), increase airway mucus secretory activity and increase vascular permeability. Prostaglandins, primarily PGD2 and PGF as well as thromboxanes, are potent vasoconstrictors. Other prostaglandins are bronchodilators.
- Tryptase, a neutral protease that is present almost exclusively in mast cells. Tryptase is believed to hydrolyze neuropeptides, stimulate the generation of kinins (e.g. bradykinins) and enhance the proliferation and activation of eosinophils and basophils.

Late-phase asthma

As the inflammation continues, a "late-phase" asthmatic response occurs; i.e. for up to 6 hours after the initial insult. Through the action of the mediators previously described, a variety of other cell types migrate to the site of inflammation:

- Eosinophils, also called granulocytes; phagocytic white blood cells that contain granules. These cells are derived primarily from macrophages, large phagocytic cells. Eosinophils congregate at the site of inflammation and, as phagocytic cells, contribute over time to structural damage to the airway epithelium and endothelium.
- Basophils; white blood cells which contain secretory granules that release histamine and serotonin as well as lysosomes.
- Macrophages; large phagocytic white cells that fulfil a variety of functions at various stages of the inflammatory cascade. These functions include presentation of invading stimuli to B-lymphocytes, production of eosinophils that are central to the asthmatic process and final "cleanup" by ingesting (phagocytosing) cellular debris that results from damage to the epithelium. Macrophages are active participants in the initiation stage of asthma and continue to be important in perpetuating the chronic inflammatory state. Macrophages induce the immigration of eosinophils, whose accumulation is a central feature of asthma.
- Platelets; which are also proinflammatory by producing platelet-activating factor (PAF). PAF is derived from membrane phospholipids. PAF is formed by a small number of cell types, mostly circulating leukocytes, platelets and endothelial cells. These lipids contribute to a number of pathological processes, including inflammation, smooth-muscle tone, and gastrointestinal secretion. PAF exerts its action by stimulating G-protein-linked cell surface receptors. Subsequently, it activates phospholipase C to form inositol phosphate (IP), diacylglycerol (DAG) and arachidonic acid. These signal cascades modulate calcium ion levels inside the cell and trigger other cellular attributes involved in inflammation.

Neuropeptide neurotransmitters that are noncholinergic and noradrenergic have also been shown to play a role in asthma. Known as tachykinins, these neurotransmitters, designated as substance P, neurokinin A and neurokinin C, act through the specific receptors designated as NK1, NK2 and NK3. When stimulated, neurokinins A and C and substance P act through sensory mechanisms to cause bronchoconstriction. An important regulatory enzyme known as neutral endopeptidase-1 (NEP) is responsible for the breakdown of neurokinin. It may be that when this enzyme is not present in sufficient quantities at the epithelial surfaces, activated neurokinins have a longer and more vigorous lifespan, or perhaps the inflammatory process and hyperresponsiveness result in an overabundance of neuropeptides. It may also be the case that peptidases released by eosinophils, mast cells and neutrophils (another type of leukocyte) degrade various neuropeptides, thereby allowing neurokinins to perpetuate airway hyperresponsiveness.

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Predisposing factors in asthma development

Genetic predisposition: studies published to date have, despite methodological problems, revealed that inheritability of increased serum IgE levels can be documented in a majority of subjects. However, it is also clear to researchers in this field that more than one gene is involved in the development of asthma. In predisposed subjects, the emergence of clinical asthma appears to require continuing exposure to allergens or repetitious insults involving viral or bacterial infections. Genes on the long arms of human chromosomes 5 and 11 have been implicated. The 5q region may be of particular relevance because it appears to contain genes that regulate the interleukin-4 gene family, IL-4, IL-3, and IL-5, and probably GM-CSF as well. Aberrant IL-4 genes may be the missing link that explains the evolution of asthma as a consequence of repeated insult from upper and lower respiratory infections. Very recently, researchers in the US and the UK announced that they had discovered a gene commonly associated with asthma. The gene, *ADAM33*, encodes a zinc-dependent metalloproteinase but, at this stage, it is not known exactly how variants of *ADAM33* influence asthma development (*Nature* 418: 426-430).

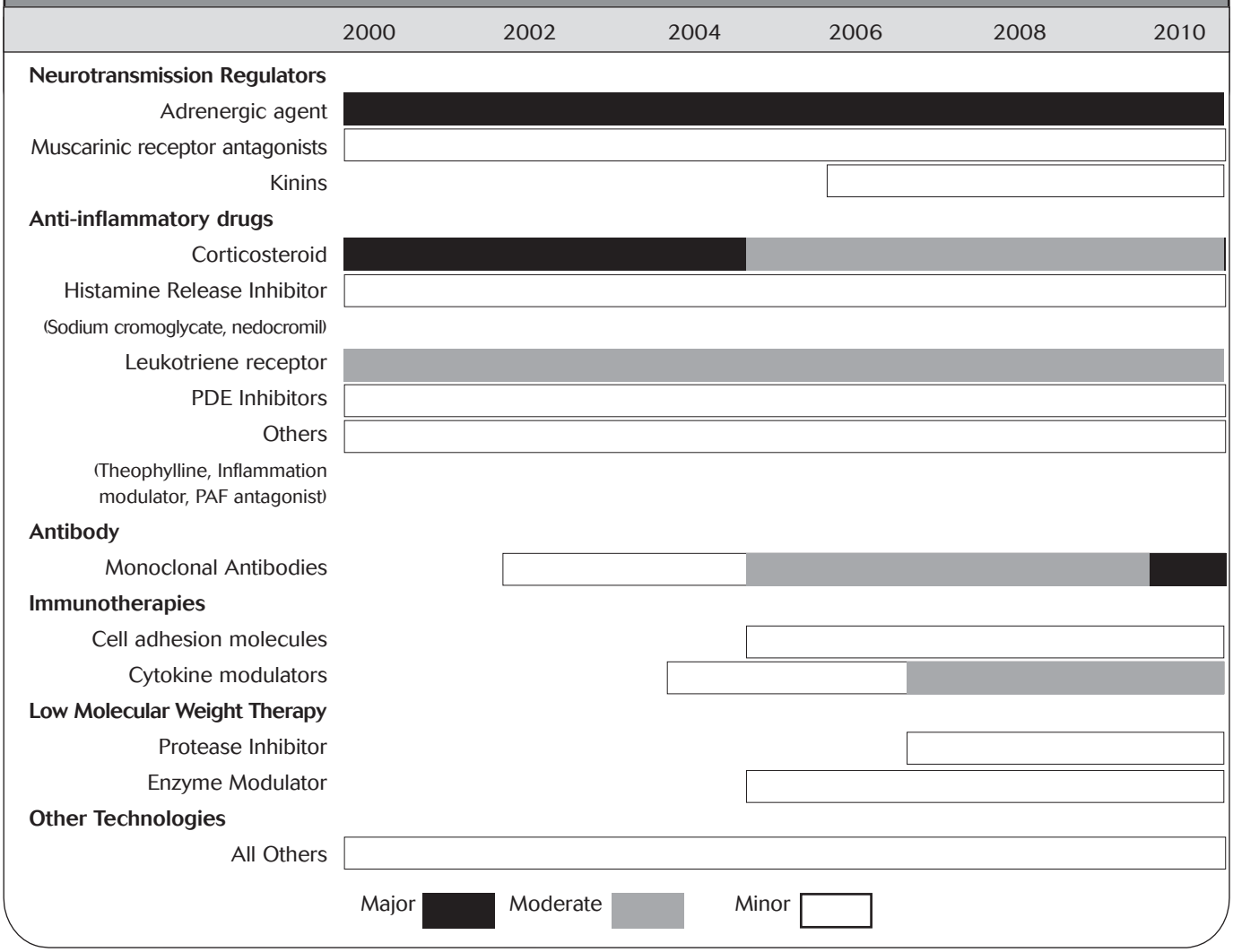
Viral infection: there is little substantial evidence that viral infections directly cause asthma, although the initial infection with a respiratory virus may sensitize the tissues to further exposure with allergens. Respiratory syncytial

virus (RSV) and influenza are the most prevalent viral illnesses in infants and young children and have been suggested as possible asthma triggers. In accordance with this idea, many adults report that their asthma symptoms were initiated by an upper or lower respiratory infection. One hypothesis proposes chlamydial pneumonia as a causal factor in adult-onset asthma. Certainly, in established asthma, infections exacerbate symptoms.

Pharmacological Management of Asthma

Asthma specialists in the US have reached a consensus on the long-term management of asthma that was published in 1997 by the National Heart, Lung and Blood Institutes in the *National Asthma Education and Prevention Program* (NAEPP). This program stresses the daily use of long-term anti-inflammatory medication with the goal of preventing chronic symptoms and maintaining nearly normal pulmonary function with normal activity. Pharmacologic intervention is used initially at a higher level than the patient's symptoms indicate with a "step-down" procedure to reach the minimal doses that achieve the goals. Daily medications required for the moderate to severe persistent categories of asthma are the long-acting inhaled β_2 agonists as well as inhaled or systemic corticosteroids. Theophylline is an accepted, but not preferred, alternative to the β_2 agonists in the more severe categories. For mild asthma, if daily medication is needed, nedocromil or inhaled corticosteroids are usually prescribed. It is for these categories that the newer leukotriene modifiers are being

Figure 1. US Forecast Asthma Management – By Technology Type



considered. Immediate relief or "rescue" for patients is provided by the β_2 agonists or adrenergic agents.

Product Technology Evaluation and Forecast

There is more effort being put into developing novel therapeutics for asthma than for any other disease involving the respiratory system, for the following reasons. First, the long-term chronic nature of the disease in many individuals indicates a need for better treatment. In a substantial number, asthma begins in childhood. Second, a significant percentage (5–10%) of the population is affected and the incidence of asthma is increasing. Third, an increased understanding of the inflammatory basis for the disease has spurred the search for new treatments and combinations of drugs, not only to alleviate symptoms but also to reverse damage to the airways. The NAEPP guidelines for treatment reflect a more thorough understanding of the disease mechanism and are shaping the market for asthma treatment. The forecast of impact of various technologies in asthma treatment is illustrated in figure 1 and discussed below.

Inhaled β_2 agonists: this drug class will continue to dominate asthma "rescue" treatment because of relative safety and ability to provide immediate relief. Nothing with this property has yet been developed that will replace drugs from this class. Long-acting β_2 agonists are available for daily treatment of moderate to severe asthma or for prevention of nocturnal symptoms.

Anticholinergic agents: anticholinergic drugs such as ipratropium bromide, a muscarinic receptor antagonist, may be used if patients are intolerant of β_2 agonists, but they have slower onset of action and are generally not as effective as β_2 agonists. Therefore, anticholinergics have a minor role in asthma treatment.

Neurokinin antagonists: compounds from this drug class affect only the late-phase response in asthma. But, because the presence of excess neurokinins is associated with hyperresponsive airways, these drugs may ultimately find a small niche in treating those patients whose asthma is not completely controlled by anti-inflammatory drugs.

Corticosteroids: the increased use of corticosteroids over the last decade has improved the condition of many patients by modulating the inflammatory process. Several corticosteroids have already been launched for asthma treatment and a few programs in late-stage studies are designed for inhaled delivery. This delivery method should considerably reduce the toxicity and risks of these drugs, with respect to bone development in children. Thus, corticosteroids will continue to play a dominant role into the next decade, until strategies to intervene at early steps in the allergic response begin to take their place.

Histamine-release inhibitors: the histamine-release inhibitors sodium cromoglycate and nedocromil, also called mast-cell stabilizers, control inflammation by preventing the release of histamine from activated mast cells. Because they are less predictably effective, their use will not increase. However, because of their good safety profile, they will continue to play a moderate role in asthma treatment.

Leukotriene receptor antagonists: the newest drugs to enter the market for asthma treatment are the leukotrienes, which include the leukotriene receptor antagonists (LTRAs) and the 5′-lipoxygenase inhibitors. The LTRAs have demonstrated some early promise in fulfilling the need for drugs to treat the inflammatory process and reverse the progress of asthma. They are perceived to be safe, in contrast to corticosteroids, with the greatest potential benefit in children under age six. Originally thought to be indicated perhaps only for mild to moderate asthma, clinicians are now beginning to prescribe these drugs for more severe cases. Their effect seems to be most obvious in the more severe cases. Thus, their use should continue to increase over the next several years to eventually play a major role. However, when newer approaches using monoclonal antibodies and small-molecule drugs to modulate the course of asthma begin to take their place in treatment, the role of the LTRAs will decrease again.

5′ Lipoxygenase inhibitors: the 5′ lipoxygenase inhibitors (5-LOs), on the other hand, have been relatively disappointing. These drugs affect an earlier step in the leukotriene synthesis pathway. However, the first 5-LO on the market, **Abbott Laboratories**'s zileuton (Zyflo), has been associated with liver toxicity in some patients, and this has dampened enthusiasm for its use. Development of second-generation compounds is moving forward but it appears that this class of drugs will not become more prominent in asthma treatment.

Phosphodiesterase inhibitors: sustained-action theophylline (a methylxanthine) continues to be a very popular pharmacologic agent throughout the world. Theophylline acts as an adenosine antagonist, affects calcium flux and is thought to function by inhibiting phosphodiesterases (PDE). The major drawback of theophylline is that it has a significant potential for causing serious side effects. This has spurred a large number of development programs in the area of PDE antagonists, particularly PDE IV, for the treatment of asthma. Several PDE inhibitors have progressed more

slowly through clinical development than was anticipated. Therefore, it may take longer for these compounds to reach the market and they will probably have lower efficacy than originally expected. Although PDE inhibitors are unlikely to achieve a dominant role, they may play a minor one.

Phospholipase inhibitors: due to a much better understanding of the role of phospholipases in the generation of eicosanoids, interest in the development of phospholipase inhibitors has rekindled. However, development is at the very early stage and it is too soon to predict whether they will be successful.

Monoclonal antibodies: the use of monoclonal antibodies, especially **Genentech**'s anti-IgE monoclonal omalizumab (Xolair) to prevent the binding of IgE to mast cells in lung epithelium, is showing promise. Intervention at the earliest stages of the allergic response in asthma is likely to prevent further serious complications and has demonstrated efficacy in phase III studies. If side effects, such as anti-idiotypic antibodies, are not a problem with treatment in the trials then omalizumab may become a preferred method of treatment. Although antibodies will probably be costly when they come to market, they should command a good position initially and attain a moderate impact in the future. Several current programs focusing on monoclonals against IL-4, IL-5, and TNFα will ensure a continuation of this method for asthma treatment through the next decade.

Cytokine antagonists: cytokine antagonists are also being developed with a similar goal – interfering with the binding and signalling via the cytokines mentioned above as well as IL-8. This is another promising approach to limiting the cascade of inflammatory responses in asthma. Because they may not be as effective as the anti-IgE approach, they are judged to have only a minor impact initially. However, this position would improve if they demonstrate the ability to permanently alter the Th-2 asthmatic response.

Finally, compounds designed to block cell interactions by binding to adhesion proteins may also have a minor role, although these compounds are all at the preclinical stage at this time. It is also likely that combinations of these blockers or inhibitors will further enhance their use.

Novel approaches

A rational approach to the development of drugs for asthma is to use the structures of the proteins involved in the inflammatory cascade to design drugs that bind and block their actions. Targeting enzymes involved in lymphocyte activation represents an extremely promising approach to immune suppression. In addition, blocking the activity of enzymes that mediate tissue damage, such as tryptase, is also likely to be an effective way to modulate and prevent the progression of asthma. Therefore, these compounds and their competing programs in development are likely to have a minor to moderate impact on treatment.

Antioxidants and surfactants are beginning to show utility in the treatment of respiratory diseases such as cystic fibrosis and respiratory distress. Thus, they are also being considered for asthma. Originally shown to be useful for acute respiratory distress syndrome, these compounds are also finding utility in preventing damage in conditions such as asthma. It is likely that the ability of antioxidants and surfactants to protect epithelial surfaces in the lungs could allow physicians to intervene with other drugs to prevent progression of asthma and even reverse its course. Thus, antioxidants and surfactants may grow in their strength in asthma therapeutics.

Competitive Developments and Implications

Development of new drugs for asthma therapy has been active in recent years and is expected to remain so over the next several years. Market sales have experienced single-digit growth in recent years but new product introductions are expected to stimulate growth in the coming years. Anti-inflammatory technologies had the single largest block of dollar sales in 2001, accounting for 70% of the total market for asthma therapy drugs. Anti-inflammatories will continue to be the dominant technology through to 2006 and will not lose much ground to other technologies. Corticosteroid products had the largest sales in the anti-inflammatory technology group in 2001, accounting for 40% of total volume. Corticosteroids will maintain their position in 2006, but will lose some market share to other technologies. Adis Business Intelligence expects that the combination adrenergic/corticosteroid products, which combine elements of the top two monotherapy formulations, will be the new drugs with the greatest market impact.

Table 1 provides historical and forecast asthma drug therapy sales for the 10 leading companies in the US asthma market. **GlaxoSmithKline** (GSK) holds the number one position with almost 40% of the volume in 2001, although Adis Business Intelligence expects GSK's share to decrease to 34% by 2006. However, not only is

Table 1. Historic and forecast US sales by leading manufacturer

Manufacturer	1998	1999	2000	2001	2001 Market Share	2002	2003	2004	2005	2006	2006 Market Share
Abbott	11	30	45	46	1.2	49	51	53	56	59	1.2
AstraZeneca	456	591	571	611	16.5	642	674	731	778	832	16.3
Aventis	315	266	201	192	5.2	209	233	261	278	311	6.1
Bayer	58	24	15	16	0.4	17	17	18	19	21	0.4
Boehringer Ingelheim	105	105	100	95	2.6	90	86	81	77	76	1.5
GlaxoSmithKline	764	906	1184	1371	37.1	1434	1501	1572	1646	1726	33.7
Novartis	1	1	1	0	0.0	1	1	2	3	5	0.1
Pfizer	1	1	1	1	0.02	1	1	1	1	1	0.02
Schering-Plough	432	319	239	227	6.1	235	238	256	272	299	5.8
All other	397	671	1006	1140	30.8	1267	1431	1552	1661	1785	34.9
Total Asthma	**2539**	**2913**	**3362**	**3698**	**100.0**	**3944.0**	**4233**	**4527**	**4791**	**5115**	**100.0**

GSK expected to maintain the number one brand in both adrenergic and corticosteroid therapy, it is expected that it will quickly dominate the adrenergic/corticosteroid combination therapy as well. **AstraZeneca**, with sales that put the company in the number two position, stays even during this time frame. **Aventis** brands are not expected to do as well and company share will only increase slightly, from 5% in 2001 to 6% in 2006.

Aventis and **Schering-Plough** both have the most launch programs for new asthma therapy drugs through to 2006, each having four programs. AstraZeneca and **Novartis** are right behind them with three programs each. Aventis has the largest development program for new asthma therapies and is expected to launch four products; one in 2002, two in 2004 and one in 2006. However, none of Aventis' late-stage programs are breakthrough and its marketing effort is not expected to generate above-average performance; therefore, sales will probably grow only moderately. AstraZeneca and Novartis also have fairly active development programs. However, like Aventis, their late-stage products are not breakthrough so sales growth will depend on marketing effort. ■

Table 2. Projected new product launch activity by manufacturer and year through 2006

Manufacturer	1998	1999	2000	2001	Total (1998-2001)	2002	2003	2004	2005	2006	Total (2002-2006)
AstraZeneca	1				1			3			3
Aventis						1		2		1	4
Bayer										1	1
Boehringer Ingelheim										1	1
GSK										2	2
Novartis			1		1	1				2	3
Schering-Plough			1		1	1		1		2	4
Total	**1**	**0**	**2**	**0**	**3**	**3**	**0**	**6**	**0**	**9**	**18**
All other	0	0	0	1	1	4	0	3	0	8	15