NOVARTIS AG
Form 6-K
February 09, 2009
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SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

FORM 6-K

REPORT OF FOREIGN PRIVATE ISSUER
PURSUANT TO RULE 13a-16 or 15d-16 OF
THE SECURITIES EXCHANGE ACT OF 1934

Report on Form 6-K dated February 9, 2009

(Commission File No. 1-15024)

Novartis AG

(Name of Registrant)

Lichtstrasse 35
4056 Basel
Switzerland

(Address of Principal Executive Offices)

Indicate by check mark whether the registrant files or will file annual reports under cover of Form 20-F or Form 40-F:

Form 20-F: x Form 40-F: o

Indicate by check mark if the registrant is submitting the Form 6-K in paper as permitted by Regulation S-T Rule 101(b)(1):

Yes: o **No**: x

Indicate by check mark if the registrant is submitting the Form 6-K in paper as permitted by Regulation S-T Rule 101(b)(7):

Yes: o **No**: x

Indicate by check mark whether the registrant by furnishing the information contained in this form is also thereby furnishing the information to the Commission pursuant to Rule 12g3-2(b) under the Securities Exchange Act of 1934.

Yes: o **No**: x

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GROUP REVIEW

OUR MISSION

We want to discover, develop and successfully market innovative products to prevent and cure diseases, to ease suffering and to enhance the quality of life.

We also want to provide a shareholder return that reflects outstanding performance and to adequately reward those who invest ideas and work in our company.

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GROUP OVERVIEW

Novartis provides healthcare solutions that address the evolving needs of patients and societies worldwide.

We offer a diversified portfolio to best meet these needs: innovative medicines, cost-saving generic pharmaceuticals, preventive vaccines and diagnostic tools, and consumer health products.

FINANCIAL HIGHLIGHTS

KEY FIGURES CONTINUING OPERATIONS(1) (In USD millions, unless indicated otherwise)	**2008**	**2007**
Net sales	**41 459**	38 072
Operating income(2)	**8 964**	6 781
Return on net sales (%)	**21.6**	17.8
Net income(2)	**8 163**	6 540
Basic earnings per share (USD)(2),(3)	**3.59**	2.81
Research & Development	**7 217**	6 430
As a % of net sales	**17.4**	16.9
Number of associates (FTE)(4)	**96 717**	98 200
Return on average equity (%)	**16.5**	26.4
Free cash flow	**4 301**	3 761

SHARE INFORMATION	**2008**	**2007**
Operating cash flow per share(1),(2),(3) (USD)	**4.31**	3.97
Share price at year-end (CHF)	**52.70**	62.10
ADS price at year-end (USD)	**49.76**	54.31
Dividend(5) (CHF)	**2.00**	1.60
Payout ratio of net income from continuing operations (%)	**53**	51

NET SALES, OPERATING INCOME AND NET INCOME

FROM CONTINUING OPERATIONS(2)

(Index: 2003 = 100%)

2008 NET SALES BY REGION

(% and in USD millions)

(1) Excluding discontinued Consumer Health operations divested during 2007

(2) 2007 results include exceptional pre-tax charges totaling USD 1 034 million (USD 788 million after tax) of USD 590 million for a Corporate environmental provision increase and USD 444 million in restructuring charges for the Forward productivity initiative

(3) 2008 average number of shares outstanding: 2 265.5 million (2007:2 3 17.5 million)

(4) Full-time equivalent positions at year-end

(5) Dividend payment proposed to shareholders for approval at Annual General Meeting in February 2009

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NEWS IN 2008

GROUP	Another year of record results in 2008 from continuing operations, confirming benefits of the strategic healthcare portfolio and led by strong performance of the Pharmaceuticals Division. Novartis positioning itself for continued success and growth in a challenging environment.
	Net sales from continuing operations rise 9% (+5% in local currencies) to USD 41.5 billion. Operating income advances 32% thanks to business expansion and benefits of the Forward productivity initiative launched in 2007 to improve speed, flexibility and productivity. Operating margin improves to 21.6% of net sales from 17.8% in 2007.
PIPELINE	One of the industry s strongest pharmaceutical pipelines providing novel medicines with 152 projects in clinical development (Phase I trials to registration). Many have potential best-in-class status, aiming to advance or create new standards of care. Three 2008 submissions receive accelerated US regulatory review status due to urgent health needs. Meningococcal meningitis vaccines progressing, offering potential for global health benefits.
RESEARCH	Novartis Institutes for BioMedical Research focuses on discovery projects at the intersection of powerful scientific mechanisms and greatest medical needs. Exploratory pipeline advances with 93 new molecular entities. Novartis ranks as having one of the industry s largest biologics pipelines.
PORTFOLIO	Agreement with Nestlé offers rights to acquire majority ownership of Alcon Inc., the world leader in eye care with pharmaceutical, surgical and consumer products. First step completed in July 2008 by purchasing 25% Alcon stake for USD 10.4 billion from Nestlé. Second step provides future rights for Novartis to acquire, and Nestlé to sell, remaining 52% Alcon stake held by Nestlé between January 1, 2010, and July 31, 2011, for up to USD 28 billion.
CORPORATE CITIZENSHIP	Novartis access-to-medicine programs for those in need reach 74 million patients in 2008. Value of contributions: USD 1.26 billion, or 3% of net sales. Dispersable tablet form of antimalaria medicine *Coartem* developed specifically for children. Novartis Vaccines Institute for Global Health opens in Siena, Italy, to develop vaccines for neglected infectious diseases.
DIVIDEND	Proposal for 25% increase in 2008 dividend to CHF 2.00 per share from CHF 1.60 in 2007. Dividend yield rises to 3.8%. Payout ratio represents 53% of net income.
LEADERSHIP	New Group structure as of December 2008 strengthens leadership team. Joerg Reinhardt, Ph.D., takes new role as Chief Operating Officer, reporting to Daniel Vasella, M.D. New division leaders named for Sandoz, Vaccines and Diagnostics, and Consumer Health. Group Head of Quality Assurance and Technical Operations position created. Board of Directors and Dr. Vasella agreed on the terms of a new contract extending his current roles as Chairman and CEO.

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DANIEL VASELLA, M.D.

DEAR SHAREHOLDER

I am pleased that despite the global financial crisis and the early signs of a worldwide recession that marked 2008, Novartis achieved record results both in sales and operating income of its continuing business.

Our diversified healthcare portfolio strategy underpinned our success in a difficult environment. Especially gratifying are the accelerated sales and improved efficiency of our Pharmaceuticals Division. Our newly launched medicines are transforming our portfolio and more than made up for the loss of a number of products in the previous year. Vaccines and Diagnostics continued to show dynamic growth, whereas growth slowed in our generics Division Sandoz. Consumer Health achieved its targets.

On a comparable basis, excluding the sales and operating income of the nutrition businesses we divested in 2007, the Group results were:

- Net sales from continuing operations rose 9% (+5% in local currencies) to USD 41.5 billion.

- Operating income grew 32% to USD 9.0 billion.

- Net income rose 25% to USD 8.2 billion and basic earnings per share increased 28% to USD 3.59.

The performance of the **Pharmaceuticals** Division exceeded the expectations of the market and increased net sales by 5% in local currencies to USD 26.3 billion. This growth was realized not only in new markets, but also in Europe, where key products most notably in Oncology posted double-digit growth rates.

The successful market launches of more than 11 products in the United States, European Union, and around the world contributed USD 2.9 billion to net sales in 2008. In addition to sustained growth of our antihypertensives and cancer medicines, the most successful innovative new products include *Aclasta/ Reclast* (USD 254 million), the only osteoporosis treatment given in a once-yearly dose, and *Lucentis* (USD 886 million), the only treatment proven to preserve and, in some cases, improve the eyesight of patients with age-related macular degeneration.

The **Vaccines and Diagnostics** Division achieved dynamic growth in net sales and continued to make significant investments in the development of the new meningitis vaccines *Menveo* (serogroups A, C, W-135 and Y) and MenB (serogroup B), as well as other innovative vaccines. Millions of infants and young people could benefit from both *Menveo* and MenB, as tens of thousands currently die of meningitis every year, while many survivors suffer from severe long-term consequences.

In the generic pharmaceuticals Division **Sandoz**, net sales grew by 1% in local currencies to USD 7.6 billion. Sandoz presents a mixed picture. Growth was slower than in previous years. Outstanding sales increases in important growth markets such as Russia, Brazil, and Central and Eastern Europe, are in sharp contrast to declining sales in the United States and some West European countries. Delays in new launches and price erosion are the main reasons for stagnation in these markets. In Germany, Sandoz is the leading generics company and is gaining further market share. As a result of price cuts, however, the market has contracted and competition has become tougher. On the positive side, Sandoz is in a pole position in biosimilars. In the future, it will be crucial

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that we are the first to launch new products and that Sandoz further extends its leading position in biosimilars.

With increased net sales of 4% in local currencies to USD 5.8 billion, the **Consumer Health Division** met its targets and also gained market share in several segments. The most important driver of growth was CIBA Vision, which under new leadership launched a number of new products and resolved its prior supply and delivery challenges. Animal Health also achieved good results, especially in the companion-animal business, but its farm-animal business was negatively affected by the recession. OTC is expanding rapidly in the emerging markets and in Japan. But, like other manufacturers of OTC brands, the business struggled with the economic downturn in the United States.

We achieved our strong overall performance in 2008 against a background that remains difficult, despite fundamentally robust prospects for growth. Compared to many competitors, however, our strategy of focused diversification in healthcare puts us in a better position to capitalize on growth opportunities in a number of markets and, at the same time, to spread our risks. It is interesting to note that our portfolio strategy now enjoys broad support and that a growing number of major pharmaceutical companies are also investing in generic pharmaceuticals.

It is gradually becoming clear that, like all entrenched dogmas, the usual comparison of companies that are pure plays with so-called conglomerates fails to present the real strengths and weaknesses. It is obvious that a strategy of unfocused diversification is bad, because you are in unfamiliar territory up against competitors with a much stronger concentration on core competencies. However, I believe that Novartis has pursued a different path, one of focused diversification that also allows us to develop our core business, which both differentiates us and adds value.

Thanks to our strategy, in 2008, Novartis stayed on course and completed several targeted acquisitions and strategic investments that both strengthened the portfolio and enhanced our internal growth drivers. For example, Novartis acquired a 25% stake in Alcon, the world leader in eye care. This transaction is part of an agreement that offers Novartis the opportunity to acquire a majority holding in Alcon.

With the purchase of Protez Pharmaceuticals, a privately owned US biotechnology company, Novartis acquired the rights to PTZ601 in Europe and the United States. This very promising antibiotic in Phase II development has the potential to treat life-threatening nosocomial infections.

Novartis also acquired Speedel Holding AG, a company in which we already had a minority stake. This essentially allowed us to acquire all the rights to *Tekturna/Rasilez*.

Despite cost pressures, the demand for medicines and treatments will nevertheless continue to rise. This demand will be driven by the following factors:

• **An aging world population with an increased need for medical care.** This continuing trend is important because, after age 55, there is an exponential rise in chronic disorders such as degenerative diseases of the joints, the cardiovascular system, and the central nervous system. The risk of cancer also increases with age. The impact of disease also heightens with advancing age due to co-morbidity. For example, over 80% of 80-year-olds suffer from at least one disease, and more than 60% suffer from two or more diseases.

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- **Unhealthy lifestyles and environmental pollution increase the frequency of chronic diseases.** Changes in eating habits and lifestyles that include very little exercise, as well as pollution especially air pollution are taking their toll in obesity, chronic cardiovascular diseases, diabetes, cancer and lung diseases.

- **Economic growth in emerging markets with improved access to medicines.** Economic growth that despite the financial crisis remains relatively robust in countries with large populations such as China, creates disproportionately high growth in demand for better healthcare in these countries.

- **Scientific and technological advances** allow new approaches in drug research that create the foundation for innovative medicines for hitherto untreatable diseases.

The cost increases associated with the growing demand for healthcare services, diagnostics and medicines lead to political activities aimed at reducing expenditures on medicines, via price reductions and generic substitution. Unfortunately, these efforts go even further and also encompass attempts to weaken patents and intellectual property. This increases the risk that long-term investment in research and development will decline. Effective medicines ultimately offer the most cost-efficient treatment for a patient and for lowering costs for the healthcare system. The weakening of protection for innovation with potential curtailment of research and development, will not lower costs in the long run, but will instead lead to massive increases in costs not to mention the human suffering. In short, the best way of reducing the long-term costs of healthcare is to provide incentives for sustainable investment in successful research and development. Without better prevention and innovative medicines, the costs of treating patients with cardiovascular diseases, cancer, diabetes or dementia not to mention other diseases will skyrocket.

The past year was marked by a severe financial crisis and recession. The recession will likely intensify over the current year and leave deep scars on the economy and the sociopolitical climate. The healthcare sector will not be spared, although it is considered a defensive sector and generally much less affected by economic factors than other industries. The pressure on prices will continue to increase because public funding (and in many countries also private budgets) will be constrained by dramatic levels of debt. This year we expect new policies from the incoming US administration, which wants not only to provide all its citizens access to medical care, but also to stem the rising costs of its healthcare system.

To provide cost-effective healthcare, all systems around the world must achieve three goals: quality assurance in diagnosis and treatment, access to all essential medical services and medicines, and financial sustainability. This requires greater transparency and comparability of treatment results with standardized treatment methods, measurement, databases and information technology systems. There has been little meaningful progress to date in these areas not only because systemic analysis and planning have been lacking, but also because politicians have been focused on short-term success. Moreover, there are many groups who are resistant to any fundamental change in healthcare.

Criticism of markets and corporations will likely increase over the next few years, extending among some, to a questioning of the principles of a free-market economy and capitalism. One thing is certain: The state has positioned itself as the only actor capable of engendering trust amidst the current financial crisis. There is a risk of a growing belief in state intervention, and the temptation to extend the capacity and scope of state responsibility in naive and dangerous ways. This is also true in the field of corporate governance. We have witnessed a shift in power from management to the board of directors, and then from the board of directors to shareholder activists. Lawmakers are increasingly influenced by activists who seek to restrict the actions of corporations, their owners and their representatives. I question whether these pressures reduce risks. They do, however, curtail the freedom of companies a disturbing development even if it stems from the best of intentions.

Optimism for the future and faith in progress will erode if freedom and risk are increasingly associated with chaos and failure. In a fast-moving modern world, some believe that restrictions promise order and therefore engender a feeling of security and protection. This is a fallacy. The erection of walls either intellectual or economic ones only further heightens the crisis. It is more important than ever before, that we endorse open markets, multilateralism and embrace a point of view that sees the opportunities of globalization and not only the threats. In a society in which control and order are valued most highly, a mentality of entitlement, coupled with hostility to reform and innovation will triumph.

Society has every reason to believe in the power of innovation. Over the last 40 years, we have witnessed a significant reduction in mortality due to numerous diseases. Deaths resulting from rheumatic fever and rheumatic heart disease have fallen by more than 60%, while deaths from hypertensive and ischemic heart disease have fallen by more than 40%. There has been impressive progress in reducing the number of patients who die from cancer. The results

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are especially striking in children, as over the last 25 years, mortality has more than halved. Moreover, medicines are responsible for 40% of the increased life expectancy and have helped to reduce chronic disability in seniors by 25% over the last 25 years.

Our **pipeline** continues to make encouraging progress, and this success not only gives me cause for optimism, but is also in line with our corporate social mission. In research, Mark Fishman and his team have discovered many new biologic targets and 93 highly promising new molecular entities. For the first time, promising new compounds for the treatment of motor disturbances associated with brain disease, cancers and bone metastases that are difficult to treat, metabolic disorders, and juvenile rheumatoid arthritis have entered clinical trials. Our scientists are currently engaged in 152 projects in various stages of clinical development. These include our new cancer medicine *Afinitor* (everolimus, formerly RAD001). In patients with advanced kidney cancer who did not respond to any of the standard treatments, this product has shown a 70% decrease in the risk of progression. Further indications are under investigation. Also highly promising are the clinical results reported with FTY720, a tablet for the treatment of multiple sclerosis, as well as the results of QAB149 for the treatment of chronic obstructive pulmonary disease.

In 2008, Novartis was the only pharmaceutical company with three medicines under priority review by the US Food and Drug Administration. In addition to *Afinitor*, these included *Gleevec/Glivec* as adjuvant therapy in gastrointestinal stromal tumors (GIST) and *Coartem* for malaria. In December 2008, the FDA approved *Gleevec/Glivec* for this additional indication. In this context, it is important to note that, for some time, US authorities have followed much more rigorous safety requirements, and it is impossible to predict timing or chances for regulatory approvals of new medicines.

Payor influence over medical decisions in Europe and in the United States has been growing. These customers place greater emphasis on evidence that new treatments offer better results and improved cost/ benefit ratios.

As investments in research and development increase and pressure on drug prices becomes more intense, efficient cost management becomes even more important. To achieve our objectives, we need to further streamline our organization and processes so that decisions can be made more quickly and be more systematically implemented.

In the context of the economic uncertainty and volatility of the global market, it is increasingly clear that we took the right step in launching the Forward initative. We exceeded our own savings targets and, in some cases, we also fostered renewed growth. Our aim is to save USD 1.6 billion by 2010. The initiative also enabled us to simplify our organizational structure and accelerate decision-making processes.

Our business success allows us to continue our **corporate social responsibility** activities. With our unique malaria and leprosy programs, we have provided more than 200 million treatments since 2001 and helped to save the lives of more than 500 000 people.

Last year, we also launched the Novartis Vaccines Institute for Global Health (NVGH), a nonprofit research institute in Siena, Italy, dedicated to the development of vaccines for patients in developing countries.

Our commitment to patients is an integral part of our strategy. The same is true of the ethical principles anchored in the Novartis corporate culture. I am most pleased that The Dow Jones Sustainability Index recognized Novartis as healthcare super sector leader in 2008. The indispensibility of these principles has become even more clear over the last few months as we are all burdened by the irresponsibility of certain actors in the financial sector which has deeply harmed the global economy.

The promotion of talented leaders to key management positions is critical to the **future success of the company.** In November, Joerg Reinhardt assumed the new position of Group Chief Operating Officer reporting to me. Joerg Reinhardt is succeeded as Head of Vaccines and Diagnostics by Andrin Oswald, previously CEO of Speedel and Global Head of Pharmaceutical Development Franchises in Pharmaceutical Development. The Board also appointed George Gunn Head of the Consumer Health Division, in addition to his role as Head of Animal Health. He replaces Thomas Ebeling, who decided to pursue his career outside Novartis. During his tenure with Novartis, Thomas Ebeling made outstanding contributions, and I would like to take this opportunity to express my sincere thanks to him. Andreas Rummelt assumed the newly created position of Group Head of Quality Assurance and Technical Operations and remains a member of the Novartis Executive Committee. Jeff George, formerly Head of Emerging Markets in the Pharmaceuticals Division, is the new Head of Sandoz. David Epstein now heads a new unit focused on the development of innovative molecular diagnostics in addition to his responsibility as Head of Oncology.

William George, member of the Board of Directors, has decided not to stand for reelection at the next Annual General Meeting. At this meeting, the Board of Directors will propose that Dr. William Brody be elected to the Board of Directors. Dr. Brody served until recently as president of Johns Hopkins University and is now president of the Salk Institute.

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As a shareholder, you are naturally interested in the further development of our company. Our ten-year total shareholder return, including dividends, which we have continuously increased, and business spin offs, surpasses that of the global market, the pharmaceutical industry index, and the performance of key competitors. The tumultuous stock market of 2008 also made it clear that we are seen as a defensive stock delivering strong performance. This view has been supported by the fact that we managed to weather the financial crisis and remain intact both operationally and in our investment activities thanks to our conservative strategy focused on sustainability.

In 2009 we anticipate another year of record results in net sales and earnings. All the elements for success are in place: products, resources, creative thinking, a determination to succeed through an even greater focus on our customers, as well as a competent management team that is distinguished by ambition and integrity.

I expect Joe Jimenez and the management team of the Pharmaceuticals Division to take advantage of the strong performance in the years ahead by investing in research and development, growth products and strategic markets. This will help to ensure that the Pharmaceuticals Division is prepared for the challenging period after 2012, when we can expect generic competition for our top-selling product *Diovan*. Our focused diversification strategy will also provide us with further growth opportunities beyond pharmaceuticals.

There are many changes taking place at the moment, but one thing remains constant: Patients need the best and most cost-effective medicines. I am certain that if we never lose sight of this fundamental imperative, we will succeed in meeting the major challenges of the future.

I would like to thank all our associates for their excellent work, their entrepreneurial mindset and their contributions to the achievement of our objectives. I am especially gratified that our associates understand the need to reorient our organization to a difficult and challenging environment.

Finally I would like to thank you, our shareholders, for the trust you place in our company. I am pleased to be able to propose an increase in the dividend to CHF 2.00 (+25%) at the next Annual General Meeting.

Sincerely,

/s/ Daniel Vasella
Daniel Vasella, M.D.
Chairman and Chief Executive Officer

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HEALTHCARE PORTFOLIO

Innovation is flourishing, bringing new effective treatments to patients. There are significant challenges, however, and the healthcare environment is undergoing unprecedented change.

The world s population is aging. Better healthcare treatments are needed, also prompting payors to manage costs aggressively. Advancing science and technology are enabling new drug discovery while increasing the cost of innovation. Economic growth in emerging countries is providing better healthcare access, but the poorest still lack basic medicines. Changing lifestyles are leading to higher prevalence of chronic and degenerative diseases.

Our strategy is to provide healthcare solutions that address the evolving needs of patients and societies worldwide.

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HEALTHCARE PORTFOLIO OVERVIEW

We believe our portfolio best meets the varied and often complex needs of patients and societies. Novartis is positioned to lead in innovation, partner with others and offer solutions to patients across a broad healthcare spectrum. In addition, a diverse portfolio reduces financial risk, bringing greater value to those who invest in our company.

Novartis has been transformed since its creation in 1996 when only 45% of net sales came from healthcare into a leader focused on fast-growing areas of healthcare.

Novartis is currently organized into four divisions:

- Pharmaceuticals: Innovative patent-protected medicines
- Vaccines and Diagnostics: Human vaccines and diagnostic tools to protect against life-threatening diseases
- Sandoz: Generic pharmaceuticals that replace branded medicines after patent expiry and free up funds for innovative medicines
- Consumer Health: Readily available products that enable healthy lifestyle choices: OTC (Over-the-Counter), Animal Health and CIBA Vision.

NOVARTIS IS NOW A LEADING HEALTHCARE COMPANY

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NET SALES BY DIVISION (1)
(Index: 2003 = 100%, Vaccines and Diagnostics since 2006 acquisition)

OPERATING INCOME BY DIVISION (1)
(Index: 2003 = 100%, Vaccines and Diagnostics since 2006 acquisition)

2008 NET SALES BY DIVISION
(% and in USD millions)

2008 OPERATING INCOME BY DIVISION
(% and in USD millions)

2008 NET SALES BY REGION

(% and in USD millions)

(1) Excluding discontinued Consumer Health operations divested during 2007

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EMERGING MARKETS: BUILDING FROM STRENGTH TO CAPTURE GROWTH

Emerging markets represent a major growth opportunity for Novartis. Growth in healthcare expenditure, fueled by enormous unmet medical need, is outpacing economic expansion in China, India, Russia and Brazil. The dynamic performance of Novartis in emerging countries during 2008 reflects solid positions built over decades as well as increased investments targeting a wide range of scientific and commercial activities. Acknowledging the diversity among emerging countries, Novartis is assessing a number of strategic models tailored to local conditions and the Group s position in each country.

In 2008, emerging countries delivered robust double-digit net sales growth for Novartis. The strategic importance of these markets will increase further in coming years amid slowing growth in the United States and Western Europe.

Though performance of these emerging markets may fluctuate, their potential for Novartis reflects solid positions built over decades, as well as increased investments targeting a wide range of scientific and commercial activities.

One example is the biomedical research and development center under construction in Shanghai, China, a significant investment focusing on infectious causes of cancer that are endemic in Asia. We re looking for great scientists, and China has an incredible pool of talent. We would ignore it at our peril, says Mark Fishman, M.D., President of the Novartis Institutes for BioMedical Research and member of the Executive Committee of Novartis.

Another example is Brazil, where Novartis is the only global pharmaceutical company with local production of active pharmaceutical ingredients. Stimulating chemical production is a key policy goal of the Brazilian government. During the past three years, Novartis has invested to expand capacity at a manufacturing site in Resende, Brazil, creating 200 new jobs. Resende exports an important chemical precursor used in the manufacture of *Diovan*, the world s best-selling branded antihypertensive medicine. Expansion of the Resende site reinforces the position of Novartis as Brazil s largest international pharmaceutical company.

Sandoz, the generic pharmaceuticals Division of Novartis, is also the leading generics company in Central and Eastern Europe and continues to outgrow competitors in the region. You see burgeoning economic growth in these countries and expenditure on healthcare is rising even faster, says Andreas Rummelt, Ph.D., Group Head of Quality Assurance and Technical Operations, member of the Executive Committee of Novartis and Head of Sandoz until December 1, 2008. And when people spend on medicines, they go for generics first.

In Turkey, Novartis is also the largest international pharmaceutical company and number two overall. Novartis has been active in Turkey for more than 50 years, and today four local manufacturing sites supply Novartis medicines to patients in more than 80 other countries around the world.

Turkey is a young country, with more than half the population under age 25, but the demographics will shift rapidly in coming years. Our aging population, the increasing incidence of chronic diseases, and low per- capita drug consumption will be the most important trends in the Turkish market over the next five years, says Guldem Berkman, Country President and Head of the Country Pharmaceuticals Organization. She adds:

You see a clear growth path for the future.

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Emerging markets vary widely. Recognizing that diversity, Novartis is assessing a number of strategic models tailored to local conditions and requirements to accelerate growth.

These large emerging growth markets are where the US was 20 years ago, and it s a huge opportunity for us over the next decade, says Joseph Jimenez, Head of the Pharmaceuticals Division and member of the Executive Committee of Novartis. The division has created an Emerging Growth Markets (EGM) organization focusing on the biggest emerging countries. You are going to see us shift our center of gravity toward some of the faster-growing markets, significantly expand the size of our sales forces and step up clinical development activities in an effort to take businesses already growing rapidly to even higher levels.

At the same time, a unique cross- divisional model is being tested in a number of pilot markets. And in India, Novartis is attempting to build a business catering to the needs of millions of low-income people living in rural villages.

PHARMACEUTICALS: A HEAD START

In major emerging markets the Pharmaceuticals Division is stepping up investments in anticipation of sustained double-digit growth during the next decade. These markets represent the biggest opportunity that currently exists in the global pharmaceutical market, says Jesus Acebillo, M.D., Head of Region Emerging Growth Markets at Novartis. Projected growth for the EGM markets is about 12% per annum, more than double the anticipated growth in the rest of the world. By 2020, sales of prescription medicines in EGM markets are expected to reach USD 400 billion, or 20% of global prescription drug sales, up from an 8% share today.

Growth of healthcare investments has outpaced the rapid economic expansion in China, India, Russia and Brazil in recent years. That momentum is likely to be sustained, despite the current global economic downturn, because of the yet-uncovered medical need of the population in these countries.

Large and growing middle classes are driving healthcare spending. Because health insurance coverage remains inadequate in most major emerging markets, patients pay an important share of healthcare costs out of their own pockets.

For all the recent improvement in economic conditions, emerging countries still face enormous unmet medical need. According to Dr. Acebillo, the frequency of cancer is expected to climb 50% in EGM markets in the next decade due to increased life expectancy. Moreover, about half of all smokers and 75% of people with high blood pressure worldwide live in EGM countries. Obesity and diabetes are growing public health challenges.

Virtually all major pharmaceutical companies today are racing to expand in the biggest emerging markets. Novartis got a head start by establishing the EGM regional organization in 2004. We accumulated a lot of valuable experience during those four years, Dr. Acebillo says.

Growth prospects are galvanized by the large portfolio of new medicines from Novartis being rolled out worldwide. We have doubled sales in the EGM countries since 2004, and we hope to double sales yet again by 2012, Dr. Acebillo says.

Because emerging markets are prone to volatility and instability, Novartis is stressing risk-management skills in development of senior executives across the EGM region. The ability to minimize risk in management of working capital and investments will be key to success, Dr. Acebillo says, together with flexible strategies that can be modified in response to abrupt changes in the operating environment.

Perhaps the biggest hurdle will be recruiting and retaining the thousands of new associates needed to meet the challenges of continued growth in these markets.

Dr. Acebillo expects a fierce battle for talent, which already is in short supply in priority EGM countries. There is a limited number of people with international experience plus language and other skills needed to work in global companies, he says.

Turkey offers a success story in talent management in an era of declining employee loyalty and active recruiting by rival companies. According to Ms. Berkman, Novartis Turkey s country president, employee turnover is about 7% per year, but only 1% among associates rated high-potential. It is essential for Novartis to remain competitive in terms of compensation and benefits, but surveys at the Turkish unit also give management high marks for empowerment and fostering a sense of responsibility for their work among associates.

As a woman heading a large company in Turkey, Ms. Berkman personifies the increasing diversity among senior Novartis managers. After graduating with a degree in chemical engineering from a prestigious Turkish university, she spent the early years of her career with international companies in the fast-moving consumer goods industry, then joined Novartis in 2001 and held positions of increasing responsibility in Marketing and Sales. She was appointed Head of Novartis operations in Turkey at the beginning of 2008.

When I started at Novartis, it was a bit challenging because most people had spent their entire careers in the pharmaceutical industry, Ms. Berkman says. But that has changed, and today it s recognized that people from different industries bring new skills that are a positive contribution to the company.

OTC: NUMBER ONE IN RUSSIA

Over the past decade, Novartis has assembled Russia s leading over-the-counter (OTC) or self-medication business, driven

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largely by growth of the OTC Business Unit but also complemented by sales of OTC products by Sandoz. It is a success story Novartis aims to emulate in other emerging markets.

Back in 1999, prospects seemed bleak. We had a very small business, 10 employees and a few brands nothing to speak of, really, recalls Dionysios Bouzos, longtime general manager of the Russian OTC unit and today Region Head Russia/India/China for the business. It was a very difficult time, following a massive banking and economic crisis in Russia the previous year. No one really knew what the future of Russia would be.

Today Russia is the fourth-largest OTC market for Novartis, measured by sales. Success factors include a tenacious local management team, strong brands and an agile response to rapidly changing market conditions. In addition, a comprehensive information system tracks sales and consumption for more than 25 000 pharmacies across Russia, untangling the underlying trends in this highly complex market.

So armed, Mr. Bouzos was able to increase geographic coverage across the huge, fragmented country while keeping costs under tight control. You marry people, the information system and analytical tools to understand the business and make the right decisions, he says.

Some of the early recruits who started as sales representatives calling on pharmacies have advanced to positions as regional managers, responsible for several territories and multi-million-dollar budgets. I don t think anyone would have imagined back then that we would come so far so fast, Mr. Bouzos says.

Novartis global brands have leading positions in the Russian market across most of OTC s strategic categories: antifungals with *Lamisil*, cough and cold with *Theraflu,* decongestants with *Otrivin* and skin irritation with *Fenistil.* In addition, *Voltaren* is Russia s number two brand in topical pain.

Russia has significance beyond its number four rank in our OTC portfolio. It provides a model for what we can and must do in other high-potential emerging markets, for example China and India, says Larry Allgaier, Global Head of the OTC Business Unit. It is a place where innovation, sales and marketing have come together to bring our goal of being the fastest-growing and most innovative OTC company to life.

The estimated 40 products poised for launch in Russia within the next three years include premium products from the global OTC pipeline as well as rebranding opportunities. A lot of secondary and tertiary Novartis brands are being given new life under global brand umbrellas, and Russia is one of the leaders in that process, Mr. Bouzos says. Sore-throat products, previously missing from the Novartis portfolio in Russia, are being piloted under the *Theraflu* brand. Other examples include *Sinecod* cough syrup, *Pulmex* chest rub and *Vibrocil*, a topical nasal decongestant available in multiple formulations.

In addition, affordable mid-tier brands are a key tool to improve access to high- quality OTC products for a wider number of consumers in Russia. The power of Novartis brands reflects a higher expectation of quality in markets in which substandard copies and counterfeits are widespread.

Another fundamental change during the past decade is the rapid emergence of sophisticated, knowledgeable and discerning Russian consumers, very engaged with their health, he adds. We have to ensure that we continue to provide the kind of innovative products such demanding customers are looking for. In Russia, innovation is an imperative, not a luxury.

For all of the success so far, Mr. Bouzos cautions that Novartis must remain enormously agile to respond to emerging market trends. Changes in Russia are happening so quickly that you don t have the luxury of waiting to see the final result. There is a

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lot of scramble, he sighs. But at the same time it creates enormous opportunities to win if you are quick, resourceful and know the market.

GEM: THE BROAD HEALTHCARE MESSAGE

Group Emerging Markets (GEM), a cross- divisional organization that aims to achieve critical mass and accelerate growth in smaller emerging markets, is operating in nine pilot countries.

In these markets, the country head oversees local Novartis business as a whole, drawing on the uniquely broad portfolio of healthcare businesses to address the needs of patients, physicians, pharmacists and governments. The aim is to boost sales by capturing synergies between divisions and business units, and ensuring a joint approach to key stakeholders and customers all while pooling shared services in infrastructure and back-office areas such as finance and human resources.

Criteria used to select GEM countries included long-term potential of a market and fragmented local operations that prevented Novartis from taking full advantage of opportunities for growth. There was also a desire to test the GEM concept in multiple geographical regions.

We observed that we have markets so small that they fall below the radar screen of some divisions, says Daniel Vasella, M.D., Chairman and Chief Executive Officer of Novartis. So as a pilot, we have established multi-divisional management teams to run an integrated local business. Our customers in these countries are often structured the same way, and we believe we can hire better talent if we have a larger, more complex business to manage than separate local divisional units.

Several emerging geographies do not de facto distinguish between originator, generic and OTC drugs. With our broad Novartis product portfolio we are well-positioned to address the needs of patients for innovative medicines, prevention and affordable self- care options in the GEM countries says Andre Wyss, Head of Region Rest of World at the Pharmaceuticals Division but Head of GEM until December 1, 2008. Aligning promotional and commercial activities with synchronized initiatives for the total Novartis portfolio leads to increased presence and share-of-voice with key stakeholders, which ultimately improves awareness of our medicines.

This new model already has driven performance in various markets and allows for optimization of initial investments in countries where Novartis previously had a minimal presence. In 2008, aggregate year-on-year growth in GEM countries accelerated to 26%, compared to 11% the previous year.

In Malaysia, Novartis Pharmaceuticals was the strongest division, well supported by its line functions. But the creation of GEM opened an opportunity to use those resources to support and drive growth of other divisions and business units, for example, by drawing on relationships built through key account managers in the Pharmaceuticals Division. In other countries, GEM was able to benefit from the strong platform and contacts of Sandoz to expand the Oncology business faster and more efficiently than would have been possible from the outside.

We go out and can deliver a broad healthcare message, Mr. Wyss says. When the GEM country head meets the general manager of a hospital and explains that Novartis has innovative medicines, generics, vaccines and OTC self-medication products, we become a much more attractive partner.

In Jordan, the Pharmaceuticals Division and Sandoz were selling separately to the same key accounts. Today, GEM is approaching each institution with a single voice and positioning Novartis as a healthcare leader.

For example, oncology is the main focus at King Hussein Cancer Center in Amman, Jordan. But our needs extend far beyond oncology products to anti-infectives, painkillers and even simple OTC products, says Mahmoud Serhan, M.D., Chief Executive Officer of King Hussein Medical Center. In our decision-making process we prefer to deal with one face at a supplier. By combining the forces of all its divisions, Novartis has become an ideal partner, providing us with a wide range of healthcare solutions.

HEALTHY FAMILIES IN RURAL INDIA

Yet another cross-divisional experiment is under way in India, where a small Novartis team is attempting to build a self-sustaining business model catering to the health needs of low-income people living in rural villages. The initiative, called Arogya Parivar, or healthy family in Sanskrit, combines healthcare education with the sale of affordable Novartis products through local pharmacies.

An estimated 65% of the population of India has no access to medicine despite prices that are among the lowest in the world. Novartis has recognized the commercial potential of the fast-growing rural market that represents 70% of India s population and almost 60% of national disposable income.

Arogya Parivar set out to fill that vacuum. The mainstay of the initiative is a team of 200 health advisors who fan out to villages in four states. Each health advisor completes a training program for three to four diseases and we also train them in public speaking, says Olivier Jarry, Global Head Project Arogya from mid-2006 to mid-2008.

These health advisors are not Novartis employees. Some are experienced pharmaceutical sales representatives who moved from a city back to a village; some have backgrounds in fast-moving consumer goods; and some belong to local non-governmental organizations. The mix works very well, Mr. Jarry says.

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Training emphasizes ethical standards, particularly adherence to the Novartis Parma Promotional Practices Policy. We insist that our health advisors fulfill all Novartis standards and conduct themselves as if they were Novartis employees, Mr. Jarry says.

The initial focus of the initiative has been patient education: raising awareness about healthcare, hygiene and nutrition. The first step is having people become aware of diseases and how to treat or prevent them, Mr. Jarry says. That s what s most lacking in India: qualified doctors are rare and no one talks to people in the villages about diseases.

Arogya Parivar health advisors speak to villagers about diseases from tuberculosis and skin infections to asthma, allergies or diabetes. They help people in the village to recognize symptoms, Mr. Jarry says. Periodically we hold health camps and bring in doctors who do examinations on the spot and refer people diagnosed with a disease to a doctor for treatment. Attendance at one of our health camps can range from 200 to 2 000 people. If we skip the education part, we would miss 99% of potential patients.

The basic product portfolio promoted by Arogya Parivar health advisors includes prescription medicines and OTC self-medication products selected on the basis of both medical requirements of the rural poor and affordability. Weekly treatment costs are held below USD 1.25.

To enhance affordability, Novartis modified standard package sizes of products such as calcium tablets for pregnant women. We revived an old design of a tube holding 15 pills, half the number and half the price of our smallest standard pack. It s been a phenomenal success, Mr. Jarry says.

About 120 priority districts out of more than 600 districts across India have been selected for the initial phase of the Arogya Parivar program, based on criteria ranging from population and purchasing power to transportation infrastructure and density of private doctors. Operations currently span four Indian states, Mr. Jarry says. And by applying similar criteria, it would be possible to launch initiatives similar to Arogya Parivar in other countries, he adds.

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PHARMACEUTICALS OVERVIEW

KEY FIGURES **(In USD millions, unless indicated otherwise)**	**2008**	**2007**
Net sales	**26 331**	24 025
Operating income (1)	**7 579**	6 086
Return on net sales (%)	**28.8**	25.3
Research & Development	**5 716**	5 088
As % of net sales	**21.7**	21.2
Free cash flow	**7 679**	6 292
Net operating assets	**14 812**	13 984
Additions to property, plant & equipment (2)	**1 115**	1 436
Number of associates (FTE) (3) at year-end	**53 632**	54 613

(1) 2007 results include an exceptional USD 307 million restructuring charge for the Forward productivity initiative

(2) Excluding impact of business combinations

(3) Full-time equivalent positions at year-end

PORTFOLIO REJUVENATION

(% and total net sales in USD millions)

NEWS IN 2008

Accelerating momentum in Pharmaceuticals thanks to dynamic growth in Oncology, the portfolio of high blood pressure medicines and USD 2.9 billion of contributions from recently launched products.

Net sales rise 10% (+5% in local currencies) to USD 26.3 billion, led by solid performances in Europe, Latin America, Japan and priority emerging markets. In the United States, net sales fall 2%, but returns to solid growth in second half of 2008 while overcoming 2007 challenges from the start of generic competition for four medicines and *Zelnorm* suspension.

Operating income advances 25% on the business expansion and productivity gains as well as lower exceptional charges. Research and Development investments rise 12% to advance robust pipeline, while productivity gains support new product launches and expansion in emerging markets. Operating margin rises to 28.8% of net sales from 25.3% in 2007.

Oncology (USD 8.2 billion, +14% lc) provides four of the five top-selling medicines, led by *Gleevec/Glivec* at USD 3.7 billion. Cardiovascular strategic products (USD 6.7 billion, +10% lc) advance on gains from the new high blood pressure medicines *Exforge* and *Tekturna*, while *Diovan* reaches net sales of USD 5.7 billion.

Recently launched products provide increasing growth contributions in 2008, led by *Aclasta/Reclast*, *Tekturna/Rasilez*, *Exforge*, *Lucentis*, *Exelon* Patch, *Tasigna* and *Xolair* that together accounted for more than 10% of net sales in 2008.

Promising development pipeline with 152 projects: *Afinitor* (advanced kidney cancer), QAB149 (chronic obstructive pulmonary disease, or COPD) and ACZ885 (Muckle-Wells syndrome) submitted for regulatory approvals.

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Novartis is consistently rated as having one of the industry s most respected pipelines with 152 projects in clinical development. Several of these projects, which include potential uses of new molecular entities as well as additional indications or new formulations for marketed products, are for potentially best-in-class medicines that would advance treatment standards.

The following table provides an overview of selected projects.

GLOSSARY

Project/Compound Novartis brand name for marketed products *(in italics)* or project reference code (combination of three letters and three numbers) for compounds, which are individual molecular entities.

Generic name The official International Non-proprietary Name (INN) for an individual molecular entity as designated by the World Health Organization (WHO).

Indication A disease or condition for which a compound or marketed product is in development and studied as a potential therapy.

Mechanism of action Specific biochemical interaction through which a drug substance produces its pharmacological effect.

Formulation The way in which a medicine is administered, such as via a tablet, injection, skin patch, infusion or device.

Phase I First stage of testing in humans. At Novartis, proof-of-concept clinical trials are conducted in a homogeneous group of patients, defined either as a genetic disease or by biomarkers, to assess molecular understanding.

Phase II Following successful proof-of-concept results, confirmatory trials are performed in larger patient groups to further assess the efficacy and safety of how well a compound works, including at various doses and in various indications.

Phase III Final clinical trials before regulatory submissions to test a compound against a placebo or another medicine to determine definitive efficacy and safety in patients.

Submitted Comprehensive data provided to government regulators for marketing approval.

Therapeutic area	Project/compound	Generic name	Indication
Cardiovascular and Metabolism	*Tekturna* SPC (1)	aliskiren, valsartan most	Hypertension
	Galvus	vildagliptin	Type 2 diabetes
	Diovan/Starlix NAVIGATOR	valsartan, nateglinide	Prevention of new-onset type 2 diabetes, cardiovascular morbidity and mortality
	Tekturna SPC (1)	aliskiren, amlodipine, hydrochlorothiazide	Hypertension
	Tekturna ASPIRE HIGHER trials	aliskiren	Renal and cardiovascular events
	LCZ696		Heart failure
	LCI699		Heart failure
Oncology	*Afinitor* (RAD001)	everolimus	Renal cell cancer (lead indication), neuroendocrine tumors, solid tumors
	Tasigna	nilotinib	Gastrointestinal stromal tumor (lead indication), newly diagnosed chronic myeloid leukemia
	LBH589	panobinostat	Cutaneous T-cell lymphoma (lead indication), Hodgkin s lymphoma, hematologic tumors
	EPO906	patupilone	Ovarian cancer (lead indication) and other solid tumors
	SOM230	pasireotide	Cushing s disease (lead indication) acromegaly, neuroendocrine tumors
	Zometa	zoledronic acid	Adjuvant breast cancer
	PKC412	midostaurin	Aggressive systemic mastocytosis (lead indication), acute myeloid leukemia
	ASA404		Non-small cell lung cancer
Neuroscience and Ophthalmics	FTY720	fingolimod	Multiple sclerosis
	AGO178	agomelatine	Major depressive disorder
	Lucentis	ranibizumab	Diabetic macular edema
	AFQ056		L-dopa induced dyskinesia in Parkinson s disease
Respiratory	QAB149	indacaterol	Chronic obstructive pulmonary disease
	Xolair	omalizumab	Allergic asthma
	MFF258	formoterol, mometasone furoate	Asthma, chronic obstructive pulmonary disease
	NVA237	glycopyrronium bromide	Chronic obstructive pulmonary disease
	QVA149	indacaterol, glycopyrronium bromide	Chronic obstructive pulmonary disease
	Glivec	imatinib	Pulmonary arterial hypertension
	QMF149	indacaterol, mometasone furoate	Asthma, chronic obstructive pulmonary disease
	NIC002		Smoking cessation
Immunology and Infectious Diseases	ACZ885	canakinumab	Cryopirin-associated periodic syndrome (CAPS, lead indication), rheumatoid arthritis, systemic onset juvenile idiopathic arthritis
	Certican	everolimus	Prevention of organ rejection
	ABF656	albinterferon alpha 2-b	Chronic hepatitis C

SBR759		Hyperphosphatemia
SMC021	salmon calcitonin	Osteoarthritis (lead indication), osteoporosis
PTZ601		Hospital bacterial infections
Mycograb	efungumab	Invasive candida
AIN457		Psoriasis
AEB071	sotrastaurin	Prevention of organ rejection

(1) Single pill combination
(2) Breakpoint cluster region-Abelson fusion protein
(3) Important receptor tyrosine kinase protein
(4) Platelet-derived growth factor receptor protein

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Mechanism of action	Formulation	Planned submission dates	Phase I	Phase II	Phase III	Submitted
Direct renin inhibitor and angiotensin II receptor antagonist	Oral	Submitted US, 2009 EU	XXXXX	XXXXX	XXXXX	XXXXX
Dipeptidyl peptidase 4 inhibitor	Oral	Submitted US (approved EU)	XXXXX	XXXXX	XXXXX	XXXXX
Angiotensin II receptor antagonist and insulin secretagogue	Oral	2010	XXXXX	XXXXX	XXXXX	
Direct renin inhibitor, calcium channel blocker (CCB) and diuretic	Oral	2010	XXXXX	XXXXX	XXXXX	
Direct renin inhibitor	Oral	2010	XXXXX	XXXXX	XXXXX	
Dual angiotensin II receptor antagonist and neutral endopeptidase inhibitor	Oral	≥2012	XXXXX	XXXXX		
Aldosterone synthase inhibitor	Infusion	≥2012	XXXXX	XXXXX		
mTOR (5) inhibitor	Oral	Submitted US, EU	XXXXX	XXXXX	XXXXX	XXXXX
Bcr-Abl (2), c-Kit (3) and PDGFR (4) inhibitor	Oral	2009	XXXXX	XXXXX	XXXXX	
Deacetylase inhibitor	Oral	2009	XXXXX	XXXXX		
Microtubule depolymerization inhibitor	Infusion	2010	XXXXX	XXXXX	XXXXX	
Somatostatin analogue	Injection	2010	XXXXX	XXXXX	XXXXX	
Osteoclast inhibitor	Infusion	2010	XXXXX	XXXXX	XXXXX	
Signal transduction inhibitor	Oral	2011	XXXXX	XXXXX	XXXXX	
Tumor vascular disrupting agent	Infusion	2011	XXXXX	XXXXX	XXXXX	
Sphingosine-1-phosphate receptor modulator	Oral	2009	XXXXX	XXXXX	XXXXX	
MT1/MT2 (6) agonist and 5-HT2c (7) antagonist	Oral	2009	XXXXX	XXXXX	XXXXX	
Anti-VEGF (8) monoclonal antibody fragment	Intravitreal injection	2010	XXXXX	XXXXX	XXXXX	
Metabotropic glutamate receptor 5 antagonist	Oral	≥2012	XXXXX	XXXXX	XXXXX	XXXXX
Long-acting beta-2 agonist	Inhalation	Submitted US, EU	XXXXX	XXXXX	XXXXX	XXXXX
Anti-IgE monoclonal antibody	Liquid formulation for injection	Submitted EU, 2009 US	XXXXX	XXXXX		
Long-acting beta-2 agonist and corticosteroid	Inhalation	2009	XXXXX	XXXXX	XXXXX	
Long-acting muscarinic antagonist	Inhalation	2011	XXXXX	XXXXX		
Long-acting beta-2 agonist and long-acting muscarinic antagonist	Inhalation	2011	XXXXX	XXXXX		
Signal transduction inhibitor	Oral	2011	XXXXX	XXXXX		
Long-acting beta-2 agonist and corticosteroid	Inhalation	≥2012	XXXXX	XXXXX		
Nicotine Qbeta therapeutic vaccine	Injection	≥2012	XXXXX	XXXXX		
Anti-interleukin-1b monoclonal antibody	Injection	Submitted EU, US	XXXXX	XXXXX	XXXXX	XXXXX
Growth-factor-induced cell proliferation inhibitor	Oral	Submitted US, (approved EU, Japan)	XXXXX	XXXXX	XXXXX	XXXXX
Interferon alpha-type activity	Injection	2009	XXXXX	XXXXX	XXXXX	
Selective binding of phosphate (Fe(III) containing polymer)	Oral	2010	XXXXX	XXXXX		
Regulator of calcium homeostasis, inhibition of osteoclast activity	Oral	2011	XXXXX	XXXXX	XXXXX	
Carbapenem antibiotic	Infusion	2011	XXXXX	XXXXX		
Antibody fragment vs. fungal HSP90 (9)	Infusion	≥2012	XXXXX	XXXXX	XXXXX	

Anti-interleukin-17 monoclonal antibody	Lyophilisate in ampule	≥2012	XXXXX	XXXXX
Protein kinase C inhibitor	Oral	≥2012	XXXXX	XXXXX

(5) Mammalian target of rapamycin protein
(6) Melatonin receptor subtypes 1 and 2
(7) Serotonin receptor subtype 2c
(8) Vascular endothelial growth factor
(9) Heat shock protein 90

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MODELING THE FUTURE OF DRUG DEVELOPMENT

Novartis scientists are accelerating development of innovative medicines with cutting-edge tools and close cooperation among multi-disciplinary teams to translate fundamental science into treatments. Novartis leads the pharmaceutical industry in completing proof-of-concept studies to confirm a medicine s mechanism of action as well as exploring multiple disease indications before full development begins. A team of Modeling and Simulation specialists is adding competitive advantage by modeling the activity of medicines and vaccines to make better decisions and reduce the painfully high failure rate for new products in clinical trials.

The pipeline of new anticancer medicines at Novartis has expanded rapidly in recent years and during 2008 six innovative drugs reached the pivotal phase of clinical testing a period of intense productivity virtually unprecedented in the field of oncology.

A key milestone came in September when the US Food and Drug Administration (FDA) granted a priority review to *Afinitor* for treatment of patients with advanced kidney cancer who have failed standard treatment. Priority reviews are expedited timelines for FDA evaluation, reserved for therapies with potential to fill significant unmet medical need.

After *Afinitor* was accepted for priority review, the FDA requested clarification of certain data as well as additional data from an ongoing trial in pancreatic neuroendocrine tumors. As a result, *Afinitor* is expected to receive a regulatory decision from the FDA within the first quarter of 2009 for patients with advanced kidney cancer.

Following a separate priority review, the FDA approved *Gleevec/Glivec* as the first therapy to reduce recurrence of gastrointestinal stromal tumors (GIST) after surgery. *Gleevec/Glivec*, a pioneering targeted anticancer medicine from Novartis, already is approved to treat chronic myeloid leukemia, primary GIST and other types of rare tumors.

Regulatory applications for *Afinitor* and *Gleevec/Glivec* also have been filed in the European Union, Switzerland and other countries, and currently are under review.

In addition to late-stage projects, we have a number of exciting early compounds in the oncology pipeline, says David Epstein, Head of the Oncology Business Unit and the new Molecular Diagnostics business at the Novartis Pharmaceuticals Division. Some of those new compounds such as our PI3 kinase inhibitors are first-in-class and have a chance to redefine cancer care across multiple tumor types.

Research and Development teams at Novartis cooperate closely to translate fundamental science into new medicines. The Translational Science group serves as the vital bridge for this teamwork, leading multidisciplinary teams in initial proof-of-concept studies of new medicines in patients. These proof-of-concept studies are designed to confirm the medicine s mechanism of action and explore multiple disease indications before full development begins.

Novartis scientists are accelerating the development of innovative new medicines with cutting-edge tools. Novartis Oncology has built a powerful team to identify and develop biomarkers substances or functions in the body that can be measured to demonstrate safety and efficacy of a medicine, or to identify patients most likely to respond positively to treatment. Biomarkers are a cornerstone of efforts by Novartis to deliver superior treatment. We believe that this is the future of Oncology, and Novartis is addressing that future today, Mr. Epstein says.

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Translational Science also underpins drug development outside the Oncology business, in therapeutic areas known collectively as General Medicines. Trevor Mundel, M.D., Global Head of Development at the Novartis Pharmaceuticals Division, has realigned management, streamlined decision-making and introduced new technologies since taking the helm in early 2008.

Benchmarking studies show that Novartis is the fastest company in the industry by a substantial margin in reaching proof-of-concept, Dr. Mundel says. Yet even if Translational Science has brought us a long way beyond where we were previously, the full impact cannot be realized without addressing the other pieces of the puzzle.

Lean and nimble biotech-style teams that drive early development at Novartis are remarkably effective in confirming whether a new drug works in somebody, somewhere, he adds. But you can t have a highly flexible entity like that tagged onto an entirely rigid, massively bureaucratic end pipe. We have to become leaner and more flexible in our approaches to late stages of development.

Dr. Mundel has delegated a pivotal role to the Modeling and Simulation team at Novartis, one of the largest of its kind in the pharmaceutical industry. The concept is simple: If Boeing and Ferrari can test their engineering feats on the computer before actually building planes and cars, Novartis can model diseases and the activity of medicines and vaccines to make better decisions and lower the painfully high failure rate for new medicines in clinical trials.

The Modeling and Simulation team already is contributing to high-priority development programs in the General Medicines pipeline such as ACZ885, a monoclonal antibody being developed as a treatment for multiple inflammatory disorders. Modeling and Simulation has become the key link between what we do in early exploratory development and the later stages of confirmatory testing, Dr. Mundel says.

For many diseases you can come up with quite nice models of what typically might happen. And because you can do that across some of the most interesting diseases we work in, sparse data that come out of Translational Science can be integrated into the model, he adds. It can give much better utility than the traditional, empirical trial-and-error approach.

AFINITOR: IN THE *GLEEVEC/GLIVEC* MOLD

Afinitor, under investigation for several cancer indications including advanced kidney cancer, epitomizes the new generation of targeted anticancer agents from Novartis modeled on the success of *Gleevec/Glivec*. *Afinitor* works by blocking the function of a protein called mTOR, a master switch in cells that serves as a hub for multiple signaling and metabolic pathways.

The mTOR pathway is mission control for proliferation in virtually every cell in the body, says Jeff Porter, Ph.D., Head of the Development and Molecular Pathways Platform at the Novartis Institutes for BioMedical Research (NIBR). Normally, mTOR is kept under tight control in the cell. But mutations in genes or other biological defects can jam the pathway in the on position, triggering the uncontrolled cell growth and proliferation characteristic of cancer.

It has taken decades to unravel the complex connections between mTOR and cancer-related pathways. *Afinitor* was developed initially as an immunosuppressant to prevent rejection of organ transplants and has been approved for that indication under the brand name *Certican* in more than 40 countries. Novartis began parallel development of *Afinitor* in cancer in 2002. The clinical program focused on patients with advanced kidney cancer who had failed standard

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therapy with treatments targeting the vascular endothelial growth factor (VEGF) pathway.

VEGF pathway inhibitors suppress angiogenesis growth of new blood vessels that tumors need to grow. *Afinitor* hits the VEGF pathway as well, but in a different way and further upstream in the tumor cell, says David Lebwohl, M.D., Head of the *Afinitor* clinical program at Novartis Oncology.

The growing numbers of patients who have failed standard therapy for advanced kidney cancer represent a pressing, unmet medical need. These are patients who have no treatment option, says Alessandro Riva, M.D., Head of Oncology Global Development.

In a study called RECORD-1, the pivotal Phase III trial on which regulatory submissions for *Afinitor* are based, patients whose cancer had worsened despite prior treatment were randomized to receive either *Afinitor* or placebo, an inactive substance made to appear like a medicine. Treatment in both groups continued until cancer once again began to progress. Initial results of RECORD-1 showed treatment with *Afinitor* more than doubled time without tumor growth and reduced the risk of disease progression by 70%. Due to the strength of these initial results, patients in the placebo group were allowed to cross over and begin treatment with *Afinitor*.

Updated results from RECORD-1 presented at the European Society for Medical Oncology Congress in September showed patients receiving *Afinitor* had no tumor growth for nearly five months versus 1.9 months for patients in the placebo group. Importantly, 25% of patients who received *Afinitor* still had no tumor growth after 10 months of treatment.

In a commentary accompanying publication of RECORD-1 results in the UK medical journal Lancet, Jennifer Knox, M.D., assistant professor of medicine at the University of Toronto, observed: A 70% reduction in the risk of disease progression or death is impressive among studies for any advanced cancer and was better than expected [for RECORD-1]. Although some questions remain unanswered, Dr. Knox added: This is strong evidence to support the anti-tumor activity of [*Afinitor*] in this population.

FROM SEQUENTIAL TO PARALLEL

The studies in renal cancer are just the beginning. The program is spearheading an initiative by Novartis Oncology for *Afinitor* to accelerate development of promising new medicines. We re taking a program that used to be fairly sequential and moving up studies in parallel to maximize the opportunity for patients, Mr. Epstein says.

During the past 18 months, Dr. Riva and Novartis medical directors around the world have coordinated studies of *Afinitor* in multiple additional indications. We now have positive results in about a half-dozen indications and we are initiating clinical trials across almost all of them, Mr. Epstein says. It s an example of the urgency we want to instill in our global Development organization. Those new indications range from breast cancer and pancreatic neuroendocrine tumors to gastric cancer and tuberous sclerosis complex, a rare genetic disorder that causes tumors to form in the brain and kidneys, and in severe cases can lead to mental retardation.

At the same time, the success of *Afinitor* in renal cancer offers a key proof-of-concept for another major development program at Novartis targeting PI3 kinase, a large family of enzymes that are important regulators of growth, proliferation and survival in virtually all cells. The PI3 kinase program at Novartis began in the late 1990s and initially focused on respiratory and autoimmune diseases. Those early programs were soon overshadowed by mounting evidence of a link between the PI3 kinase pathway and cancer. The pathway is activated when growth factors bind to receptors on the cell surface. A biological chain reaction carries the signal to the nucleus of the cell, where it stimulates synthesis of proteins needed for growth or nudges the cell-cycle machinery to initiate cell division.

Importantly, mTOR appears to be a node in the downstream branch of the PI3 kinase pathway. Novartis is the only major pharmaceutical company developing medicines targeting both the upstream (PI3 kinase) and downstream (mTOR) branches of the pathway.

The programs reflect a central tenet of NIBR research strategy: attacking multiple targets within a pathway believed to play a major role in a disease like cancer. Two PI3 kinase inhibitors discovered by Novartis have entered early development. Both target PI3 kinase as well as mTOR, while a later generation of more selective PI3 kinase inhibitors is still in preclinical development. There have been lots of debates about whether you want specificity or a dual PI3 kinase/mTOR inhibitor, says William Sellers, M.D., Head of Oncology Research at NIBR. Suffice to say that there are good reasons to have both.

COMBINATIONS AND BIOMARKERS

Combinations incorporating multiple anticancer agents have been the mainstay of oncology for decades, and combinations play a significant role in development programs at Novartis Oncology. Patients need combinations because there are multiple pathways helping their cancers grow, Mr. Epstein says. If you can knock out multiple pathways, there is more chance patients will respond better and live longer.

The broad mechanism of action for *Afinitor* makes it a potential component in many combinations. We are testing multiple opportunities in combination with current standards of care across different tumor types and different phases of the disease, Dr. Riva says. Our priority is to

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make every effort to improve the treatment of patients, and if we can achieve this through a combination of a Novartis drug with one from another company, we are happy to do that.

Novartis and Swiss rival Roche Holding AG have exchanged supplies of medicines for testing as possible combinations, including *Afinitor* with Avastin®, a blockbuster VEGF inhibitor jointly developed by Roche and Genentech Inc. I think we ll see more of this, Mr. Epstein says. As combinations become increasingly important in the treatment of cancer, companies somehow need to work together so that clinical trials of combinations can start as early as possible.

The aggressive biomarker development program at Novartis also is expected to help make new medicines available to patients faster. In late 2008, Mr. Epstein was tapped to lead a new unit focusing on development of innovative molecular diagnostics based on biomarkers.

Changes in biomarkers can be detected earlier or more readily than traditional clinical endpoints, though results based on surrogate markers normally need to be confirmed by long-term outcomes studies.

Another potential application is predicting patient response to drug treatment. Among patients sharing a common diagnosis, some may respond to a medicine while others fail to respond and a third group develops side effects. Unraveling the reason for differences in individual response would enable companies to develop diagnostic tests to help identify those patients more likely to respond to treatment, as well as those more likely to develop side effects.

The need to find surrogate endpoints and biomarkers has been clear in oncology for a long time, Mr. Epstein says. We ve been able to take a big step forward and we have biomarker programs in place for almost every drug that we have in the clinic.

GLEEVEC/GLIVEC AND *TASIGNA*: AN ALLIANCE WITH PATIENTS

The potential new indications for *Gleevec/Glivec*, including adjuvant treatment of GIST, underscore a continued commitment by Novartis to cancer patients with limited treatment options. Another example of that commitment is the development of *Tasigna*, a treatment for patients with chronic myeloid leukemia (CML) who are resistant or intolerant to existing therapies, including *Gleevec/Glivec*.

Tasigna was approved by the United States, the European Union and other countries in 2007. Approval of *Tasigna* provides more comprehensive treatment options for physicians and patients, Mr. Epstein says.

Development was exceptionally rapid: *Tasigna* went from first human trials to regulatory submissions in slightly more than two years. We were able to build on our *Gleevec/Glivec* experience, Dr. Riva says. And just as *Gleevec/Glivec* expanded from initial approval in CML to an

unprecedented number of additional indications, clinical trials have been launched to compare *Tasigna* with *Gleevec/Glivec* in patients with various forms of CML, as well as GIST.

Meanwhile, Novartis Oncology has introduced the CML Alliance, a package of diagnostic tests, programs and materials to enhance patient adherence, help improve outcomes and potentially extend the lives of leukemia patients. These tests, in turn, help physicians reach better outcomes for patients, Mr. Epstein says. Physicians would not normally have access to these tools. By putting them into the hands of doctors who actually use them, we make a real difference and distinguish Novartis from other companies.

The CML Alliance package includes tests for blood-level monitoring of patients treated with *Gleevec/Glivec*, enabling physicians to individualize dosage. Metabolism varies among individuals, and we realized that patients receiving identical doses of *Gleevec/Glivec* had different levels of the drug in their blood, Mr. Epstein adds. That s important because blood levels correlate with outcomes: Most patients with high drug levels do much better than patients with low levels.

In addition, Novartis has worked with the European Leukemia Net, a network of academic institutions and researchers, to develop standard guidelines for treatment of CML patients through the entire cycle of the disease. The guidelines have been widely adopted around the world. In 2009, Novartis plans to launch similar packages for GIST and neuroendocrine tumors, based on the initial CML Alliance model.

GENERAL MEDICINES: A NIMBLE ALTERNATIVE

In both Oncology and General Medicines, Novartis has eluded the declining productivity that has afflicted many rivals in recent years. Between 2000 and 2008, Novartis received the most FDA approvals for new molecular entities of any major pharmaceutical company.

The contribution of Translational Science has enabled Novartis to halve the average time required to reach proof-of-concept in clinical programs. Dr. Mundel is convinced that further improvement can be achieved during Phase II studies in which companies traditionally test a range of doses of a new medicine in search of initial indications of efficacy that can be confirmed in the pivotal Phase III trials.

Phase II is choking the industry, Dr. Mundel says. Often Phase II trials are actually bigger and take longer than Phase III studies, he says. And the failure rate for Phase II across the industry is extraordinarily high

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approaching 80%, according to the latest benchmarking numbers.

Novartis fares better than the industry average because drugs that do not work are filtered out earlier. But the early proof-of-concept strategy also poses challenges. Typically, our early proof-of-concept studies are done in relatively small groups of patients, so the data are sparse. How do we project that into big programs? Dr. Mundel adds.

The traditional answer for pharmaceutical companies would be a huge Phase IIB study. At Novartis, however, Modeling and Simulation provides a more nimble alternative.

Modeling and simulation begins with the creation of a mathematical and statistical model of a medicine acting in parts of the body where the disease occurs. Modelers use data from actual patients, literature data and preclinical animal data to build models, then statistically predict responses to the medicine over time.

In some programs, modeling and simulation can be a springboard directly from the proof-of-concept to Phase III. Our goal is to omit Phase IIB in up to 50% of our programs. In the remaining programs, modeling and simulation will help usto reduce the size, duration and cost, Dr. Mundel says. This is the extension of what people have always hoped to do: rational drug development, or Model-Based Drug Development, to use a term coined by the FDA.

As a Rhodes Scholar, Dr. Mundel studied mathematics at the University of Oxford and later completed graduate studies in mathematics at the University of Chicago. He is rigorous about distinguishing useful applications of modeling and simulation from exaggerated claims made by some proponents.

Models have to be infused with data and a lot of common sense and judgment. They really are dependent on how much you know about the disease and about the precedent for the drug and its mechanism of action, he cautions.

There also are elements of modeling and simulation that approximate guesswork. In particular, modeling and simulation has gotten wrapped up with the hype around systems biology. We aren t trying to model the complete, complex pathway dynamics of systems, which remain highly speculative. We re talking about modeling select components of drug pathways and the more familiar models of pharmacokinetics and pharmacodynamics.

FROM HIGH SCIENCE TO MARKET RESEARCH

The Modeling and Simulation organization at Novartis is headed by Donald R. Stanski, M.D., who, following an academic career in anesthesiology/clinical pharmacology at Stanford University, served as a scientific advisor to the director of the FDA s Center for Drug

Evaluation and Research before joining Novartis in 2005.

Basically we integrate pieces of information in a way that uses mathematics and statistics as a thread to bind, Dr. Stanski says. We want to integrate every piece of knowledge and data to make smarter decisions about whether a molecule is worth developing, and decrease the clinical-trial failure rate in Phase III.

Applications of modeling and simulation at Novartis range from esoteric high science to market research and health economics. To support development of a novel medicine for spinal cord injury, Dr. Stanski s team simulated circulation of spinal fluid, incorporating pulsations generated by heartbeat and respiration, and adjusting the model for the effect of spinal nerve roots on the flow path. The model resolved key questions about administration of the treatment into the spinal space.

Modeling and Simulation also is beginning to work closely with Strategic Marketing on development compounds, assisting in

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preparation of outcomes and health economic analysis, and integrating with portfolio analysis. Still, some of the clearest examples yet of the potential impact of modeling and simulation have come in priority development programs, including the promising monoclonal antibody ACZ885.

ROAD TO REMISSION

ACZ885 targets IL-1 beta, a key weapon in the body s immune system defenses. Excessive production of IL-1 beta is believed to play a role in diseases ranging from rheumatoid arthritis and chronic obstructive pulmonary disease to asthma and certain rare genetic diseases.

Novartis scientists chose to conduct the initial proof-of-concept study in patients with Muckle-Wells syndrome, a rare inherited disease in which a genetic mutation stimulates excess production of IL-1 beta and causes itching skin rashes, daily fever and swollen joints. (Muckle-Wells syndrome and two related disorders are known collectively today as cryopyrin-associated periodic syndromes, or CAPS.)

Muckle-Wells syndrome seemed an ideal candidate for the proof-of-concept because its pathology was uncomplicated, driven by a single, well-defined molecular defect. According to the scientific hypothesis, ACZ885 should bind exclusively with IL-1 beta circulating in the blood, halting excessive production and alleviating symptoms.

In late 2004, Timothy Wright, M.D., and Thomas Jung, M.D., from the Novartis Translational Science Group contacted Professor Philip Hawkins at London s Royal Free and University College Medical School, a world authority on rare diseases such as MuckleWells syndrome. A proof-of-concept study was jointly designed and the first patient received ACZ885 in early 2005. Three more patients were given injections of ACZ885, and all had immediate positive responses lasting, on average, about six months.

Subsequent trials have provided even more evidence of the safety and efficacy of ACZ885 in this rare disease. To date, 69 patients have received the drug, and treatment of the very first patient has continued for more than 3.5 years.

Behind the scenes, the Novartis Modeling and Simulation team, led by Philip Lowe, Ph.D., has played a crucial role in the ACZ885 program. It is the clearest example yet of how modelers can extrapolate sparse data from initial proof-of-concept studies to predictions about larger patient populations or different diseases.

Following the initial study in Muckle Wells syndrome in 2005, the Modeling and Simulation group analyzed data about the action and effects of the treatment in the body; how it is absorbed, metabolized and eliminated; and other measures of patient response.

One key question was whether ACZ885 would merely neutralize IL-1 beta or actually achieve a disease-modifying effect on patients with Muckle-Wells syndrome. Surprisingly, the resulting model indicated ACZ885 was able to decrease the IL-1 beta pathway to near normal for

about six weeks after a single treatment. Modelers then calculated that a single injection every eight weeks would hold the IL-1 beta pathway in check and keep patients with Muckle-Wells syndrome in full remission.

Applying these predictions based on data from only four patients ACZ885 advanced to a confirmatory trial. After achieving clinical remission following a single dose of ACZ885, a total of 31 patients were randomized to receive either three additional injections of ACZ885, eight weeks apart, over the following six months or the identical schedule of placebo injections.

The Modeling and Simulation group predicted none of the patients receiving ACZ885 would suffer flares, or recurrence of active disease, while more than 90% of the control group would have flares. In fact, all patients treated with ACZ885 did remain flare-free during the trial; 81% of the control group suffered recurrences.

This is our Phase III study and the outcome is an example of how powerful modeling and simulation can be for the design of clinical trials, Dr. Jung says. The data provided the foundation of regulatory applications for ACZ885 submitted to authorities in Europe and the US in 2008.

Meanwhile, in line with research strategy at Novartis, the ACZ885 program has expanded to parallel disease indications following the initial successful proof-ofconcept trial. Currently, ACZ885 is being tested or explored as a potential treatment for rheumatoid arthritis, systemic onset juvenile idiopathic arthritis and several other indications.

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AFQ056: PROBING FUNDAMENTAL MECHANISMS IN THE BRAIN

Diseases affecting the brain or central nervous system pose formidable hurdles in drug discovery. In the 1990s Novartis was one of the first major pharmaceutical companies to show an interest in a new family of brain receptors, known as mGluRs. AFQ056, a compound generated by Novartis chemists directed at the receptor target mGluR5, is in clinical trials for treatment of a complication related to therapy for Parkinson s disease. The AFQ056 program is an example of how use of drug candidates can be rapidly re-directed as more is learned about the mechanisms of disease.

Drug discovery rarely is an overnight success.

In 1990, a team of Japanese researchers identified a new class of receptors in the human brain, setting off a scientific race to translate the discovery into new medicines for disorders ranging from drug addiction and anxietyto schizophrenia and Parkinson s disease.

Novartis was one of the first major pharmaceutical companies to show an interest in the new family of metabotropic glutamate receptors, known by the acronym mGluRs. Novartis scientists generated a series of compounds directed at this target. One of these compounds, AFQ056, is directed to a specific subset of the mGluR family, termed mGluR5. An inhibitor of mGluR5, AFQ056 currently is in clinical trials for a complication of therapy for Parkinson s disease.

The story of AFQ056 reflects the innovative research strategy at Novartis. Scientists at the Novartis Institutes for BioMedical Research (NIBR) focus on both where the scientific knowledge leads, and where there is an unmet patient need. As science evolves and more is learned about the mechanisms of disease, the use of drug candidates may be rapidly redirected. The original hope for mGluR5 inhibitors was to treat anxiety. Because anxiety is a very heterogeneous disease in terms of mechanism, however, diseases with a more specific linkage to mGluR5 were sought.

Our approach is to go after diseases where there is unmet need, and we believe we understand enough about the fundamental mechanism to make an impact, says Mark Fishman, M.D., President of NIBR and member of the Executive Committee of Novartis. Once we show a medicine is safe and effective in a homogeneous population, we extrapolate that to subsets of more common diseases.

AFQ056 exemplifies that approach. Scientists from NIBR and the Translational Medicine team that directs early development tested AFQ056 in a series of proof-of-concept studies in humans and steadily narrowed the focus of the program. Based on rodent models and human post-mortem data, the team focused on Parkinson s disease levodopa-induced dyskinesia (PD-LID) as a target indication.

DISORDER OF MOVEMENT

Parkinson s disease is a disorder that usually strikes between the ages of 50 and 60. The hallmarks of Parkinson s disease are disorders of movement. Patients have a hard time initiating movement, steps become short and shuffling, and balance is impaired. Muscle stiffness limits movements and problems with speech are common. Tremor is also common, especially of the hand.

Symptoms of Parkinson s disease appear when brain cells that produce the neurotransmitter dopamine die or become impaired. Standard treatment today is dopamine-replacement therapy with levodopa,

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a natural substance that is converted to dopamine once inside the body. The introduction of levodopa in the 1960s was a revolutionary step in overcoming the symptoms of Parkinson s disease. Novartis has established expertise in the field of Parkinson s disease and markets *Stalevo*, an innovative treatment that combines levodopa with inhibitors of critical metabolizing enzymes.

Unfortunately, the majority of patients treated chronically with levodopa develop dyskinesias, rapid, irregular involuntary movements such as flinging and flailing arms which can be as crippling as the underlying disease. According to the Michael J. Fox Foundation, founded by the Canadian actor who has emerged as a leading spokesman for Parkinson s disease, approximately 80% of patients develop dyskinesias after five to 10 years of treatment with levodopa.

These dyskinesias are particularly prominent among younger Parkinson s disease patients. No effective treatment for levodopa-induced dyskinesias is yet available, and severe cases are treated with surgical methods such as deep brain stimulation. Gaining insight into ways to control or prevent dyskinesia would make a dramatic impact on the daily lives of Parkinson s patients, according to Deborah W. Brooks, a co-founder of the foundation.

PD-LID illustrates the triad of qualities we look for in a proof-of-concept study: a high unmet medical need, compelling scientific rationale and a sound medical hypothesis that can be rigorously tested in patients, says neurologist Donald R. Johns, M.D., Head of Neuroscience Translational Medicine at NIBR.

The AFQ056 project really took off after colleagues from Translational Medicine identified PD-LID as a potential indication, adds Fabrizio Gasparini, Ph.D., the chemist who led the team that discovered AFQ056 and recipient of a 2006 Novartis leading scientist award for his contributions to the program.

Diseases affecting the brain or central nervous system pose exceptional hurdles in drug discovery. We don t understand the physiology of the brain as well as we do other organs. And most major neurological diseases are chronic, debilitating disorders that progress slowly over decades. The triggers are still unknown and we lack effective diagnostic tools, Dr. Gasparini says.

It s also a challenge to deliver medicines into the brain. A barricade of densely packed cells known as the blood-brain barrier protects the brain from common bacterial infections, but it also prevents passage of potentially beneficial treatments. Even when a medicine is able to penetrate the blood-brain barrier, it is difficult to monitor the effects in the brain following treatment, Dr. Gasparini adds. An imaging technique developed by NIBR colleagues showed that AFQ056 penetrates into the brain and binds with mGluR5, and permitted better dosing decisions. That tool has been crucial to the success of the program so far. Still, formidable hurdles remain.

FINE-TUNING GLUTAMATE SIGNALS

Every idea, memory and emotion produced by the human brain is created as a series of electrical and chemical signals transmitted through connected networks of neurons. Neurons transmit these signals to one another at specialized sites of contact called synapses, junctions between two nerve cells. A synapse relays information by releasing chemical messengers, called neurotransmitters, from the sending neuron to the

receiving one where the neurotransmitter binds to related receptors, fitting snugly like a key in a lock. One of the most important neurotransmitters is glutamate, which acts by binding to the glutamate receptors, including the mGluR family.

Proper function of the brain depends on a delicate balance of signaling between excitatory and inhibitory neurotransmitters. Glutamate is one of the principal excitatory neurotransmitters. Too much glutamate signaling leads to imbalances believed to play a role in diverse brain disorders.

mGluR5 is present at key nodes in brain circuitry and under normal conditions and circumstances, mGluR5 functions to fine- tune glutamate transmission, says Graeme Bilbe, Ph.D., Global Head for the Neuroscience Disease Area at NIBR. Inhibition by AFQ056 offers an effective way to modulate the excessive glutamate transmission occurring in the brain regions involved in Parkinson s disease.

As development of AFQ056 progressed, discoveries in fundamental science added support to the hypothesis that levodopainduced dyskinesias were due to excessive mGluR5 signaling. Preparations for the proof-of-concept study of AFQ056 in the treatment of PD-LID were reinforced by the arrival of Baltazar Gomez-Mancilla, M.D., as the Translational Medicine representative on the AFQ056 team. Dr. Gomez-Mancilla brought a unique set of skills in the basic science, clinical expertise and drug development of Parkinson s disease to our interdisciplinary scientific and clinical team, Dr. Johns says.

The successful proof-of-concept study of AFQ056 was completed in May 2008. The dyskinesias were diminished in most patients. While early observations are quite encouraging, this short-term study needs verification in full development. In addition, the proof-of-concept in dyskinesias suggests potential benefit of AFQ056 in treatment of a broader spectrum of disorders linked anatomically with the basal ganglia, the region of the brain that controls movement.

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VACCINES AND DIAGNOSTICS OVERVIEW

KEY FIGURES **(In USD millions, unless indicated otherwise)**	**2008**	**2007**
Net sales	**1 759**	1 452
Operating income	**78**	72
Return on net sales (%)	**4.4**	5.0
Research & Development	**360**	295
As a % of net sales		