



combat the outbreak of A(H1N1) influenza virus is exposing the limitations of global pandemic preparedness and, at the same time, highlighting scientific, technological and commercial opportunities for a more robust public health response to the threat of pandemic influenza. The biggest opportunities involve intensified development of novel adjuvant and of innovative manufacturing methods that move beyond 60-year-old production processes that grow vaccines in chicken eggs.

Despite a large increase in manufacturing capacity over the last five years, it will probably take four years or more to produce sufficient vaccine to protect everyone worldwide using proven, approved products and technologies, according to a study conducted by the Oliver Wyman Group in collaboration with WHO and the International Federation of Pharmaceutical Manufacturers & Associations (IFPMA).

Manufacturing constraints and limitations on supplies of raw materials—principally of the chicken eggs used to incubate vaccine—will likely force public health officials in the U.S. and Europe to consider diverting resources from the production of seasonal influenza vaccine to a swine flu vaccine, or to delay mass production of a swine flu vaccine until seasonal vaccine production is completed. They will have to balance the possibility of widespread deaths from the new flu strain against the near certainty that reducing seasonal flu vaccination will increase deaths from less exotic strains of the virus. The decision is made even more complicated by the

knowledge that the emergence of a new and worrisome strain of H1N1 influenza does not diminish the risk of preserving some manufacturing capacity to cope with an avian (H5N1) influenza pandemic. Nevertheless, the development of new adjuvants, combined with increased manufacturing capacity, has dramatically improved industry's ability to respond to a potential swine H1N1 influenza pandemic, according to Rino Rappuoli, global head of vaccines research at Novartis AG. "If we had this problem five years ago, we would be in a total panic because we wouldn't know what to do." The challenge for public health officials and regulators, particularly FDA, involves making choices between relying on well tested vaccine technologies, such as nonadjuvanted, whole killed virus vaccines, or taking chances on scientifically promising but less tested approaches such as using adjuvants to stretch supplies.

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New Drugs Approved by US FDA in 2008

Xiaoqi Chen



Introduction

The number of novel drugs approved by the US FDA to enter the marketplace was slightly improved for 2008 over 2007. In 2008, the US FDA approved 21 new molecular entities (NMEs) and 3 biologic license applications (BLAs). The slight increase of approvals was still less than the approval rate seen in the 1990s. John Jenkins, director of the FDA's office of New Drugs cautions about reading too much into slight changes year to year in the number of approvals. The fact that FDA approved in the previous year should not be interpreted as a trend or FDA speeding up or slowing down; it's simply that those are the applications that met the standards for approval. A couple of applications required multiple cycles for approval and those applications approvals were delayed from previous years. It is still a challenge for companies to send their drug applications to FDA.

Nine NDA applications received priority review status out of the 21 NMEs and 3 BLAs approved in 2008, a reflection of their perceived potential to address unmet medical needs. From the perspective of therapeutic novelty, two products that attracted attention in 2008 were romiplostin (Nplate; Amgen) and eltrombopietin (Promacta; GlaxoSmithKline). These two drugs act as thrombopoietin receptor agonists targeting thrombocytopenia in patients with chronic immune (idiopathic) thrombocytopenic purpura. Additionally, riloncept (Arcalyst, Regeneron) also received fast approval as the first therapy for the rare inflammatory cryopyrin-associated periodic syndromes which resulted from excessive release of activated interleukin-1.

Regulatory Setbacks

Last year there were two high profile regulatory delays, alogliptin (SYR-322) from Takeda Pharmaceutical Company and prasugrel (Effient) developed by Daiichi Sankyo Company and Lilly. The compound is an investigational anti-diabetic drug in the DPP-4 inhibitor class. The safety and efficacy of alogliptin was studied as a once-daily monotherapy adjunct to diet and exercise and as an add-on therapy to other antidiabetic medications including sulfonylureas, metformin, thiazolidinediones (TZDs), and insulin. In the studies, alogliptin was associated with statistically significant reductions in hemoglobin A1c, which reflects average blood glucose concentration over the previous two to three months. The FDA has extended date of Prescription Drug User Fee Act (PDUFA) from Oct 2008 to June 2009. Prasugrel is a novel platelet inhibitor developed by Daiichi Sankyo and Lilly for acute coronary syndromes for percutaneous coronary intervention (PCI). Prasugrel is a member of the thienopyridine class of ADP receptor inhibitors, like ticlopidine (Ticlid) and clopidogrel (Plavix). These agents reduce the aggregation of platelets by irreversibly binding to P2Y12 receptors. Both clopidogrel and pasugrel are prodrugs, converted by cytochrome P450 enzymes in the liver to their active forms, which bind irreversibly to the P2Y12 purinergic receptor on platelets. In the clinic, the large TRITON-TIMI trial tested the two drugs head to head in

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more than 13,000 patients. The end result was that the prasugrel-treated group had fewer cardiovascular problems, but more episodes of severe bleeding. The FDA is apparently planning to discuss the drug at a February 2009 meeting of its Cardiovascular and Renal Drugs Advisory Committee. The PDUFA date was pushed back until the advisory committee meeting.

New Drugs Approved by FDA in 2008

Name: Rilonacept (Arcalyst)¹
 Company: Regeneron
 Approval Date: Feb 2008
 Indication: Cryopyrin-associated periodic syndromes

Arcalyst, a dimeric fusion protein, blocks interleukin-1 which is a signaling protein secreted by certain immune-related cells in the body. Interleukin-1 acts as a messenger to regulate inflammatory responses, but in excess it can be harmful. It has been shown that interleukin is important in the inflammation seen in cryopyrin-associated periodic syndromes (CAPS) sufferers with familial cold autoinflammatory syndrome (FCAS) or Muckle-Wells syndrome (MWS) and neonatal onset multisystem inflammatory disease. The FCAS and MWS disorders affect about 300 people in the United States. Symptoms of both of these disorders include inflammation such as joint pain, rash or skin lesions, fever and chills, eye redness or pain, and fatigue in both children and adults. In addition to these symptoms MWS is associated with more severe inflammation and may include hearing loss or deafness. Also some MWS patients may be affected by the buildup of a protein substance that damages organs and tissue (amyloidosis). CAPS disorders are inherited. Fifty percent of CAPS cases are associated with a gene mutation in the CIAS 1 gene.

The FDA based its approval on a clinical study conducted by Regeneron, which demonstrated the drug's safety and effectiveness. Using a daily diary questionnaire, 47 patients rated the following five signs and symptoms of CAPS: joint pain, rash, feeling of fever/chills, eye redness/pain, and fatigue. Patients noted initial onset of relief of symptoms in their diaries within several days. Adult patients need subcutaneous injections of 320 mg followed by 160 mg maintenance dose of the drug weekly.

Name: Certolizumab pegol (Cimzia)²
 Company: UCB
 Approval Date: Apr 2008
 Indication: Crohn's disease

Certolizumab pegol is a pegylated humanized Fab' fragment of an anti-TNF monoclonal antibody with a high affinity for TNF- α . More precisely, it is a PEGylated Fab' fragment of a humanized TNF inhibitor monoclonal antibody. Certolizumab, unlike other monoclonal antibodies such as infliximab and adalimumab, does not contain an Fc portion and therefore does not induce in vitro complement activation, antibody-dependent cellular cytotoxicity, or apoptosis. Certolizumab is the first and only PEGylated antitumor necrosis factor antibody to be approved by the FDA. The chemical addition of polyethylene glycol (PEG) to an injectable drug is designed to provide increased efficacy, reduced dosing frequency, decreased toxicity/immunogenicity, increased stability, and enhanced solubility.

In April, the FDA approved certolizumab pegol powder (Cimzia) for reducing signs and symptoms of Crohn's disease and maintaining clinical response in adult patients with an elevated baseline level of C-reactive protein (CRP) of at least 10 mg per liter who have had an inadequate response to conventional therapy. The 400 mg of drug needs to be dosed subcutaneously initially and at week 2 and 4. If the response occurs, 400 mg of drug will be subcutaneously administered every week.

Although an increased risk for tumors was not observed in certolizumab clinical studies, their limited size and duration precludes firm conclusions, and postmarketing studies will be conducted to obtain long-term safety data.

Name: Romiplostim (Nplate)³
 Company: Amgen Inc.
 Approval Date: Aug 2008
 Indication: Thrombocytopenia in patients with chronic immune (idiopathic) thrombocytopenic purpura

Romiplostim is a fusion protein analog of thrombopoietin, a hormone that regulates platelet production. It is marketed by Amgen under the trade name Nplate. Romiplostim, a peptibody, containing two components—a "binding" peptide linked to a larger protein. Peptibodies are engineered therapeutic molecules that can bind to human drug targets and contain peptides linked to the constant domains of antibodies. Romiplostim works similarly to endogenous thrombopoietin (TPO). The binding peptide component of romiplostim stimulates the TPO receptor, which is necessary for growth and maturation of bone marrow cells that produce platelets. Low platelet counts leave adult ITP patients open to sudden serious bleeding events, making it impossible to arrest blood flow. The risk for serious bleeding events

increases when platelet counts drop to less than 30,000 platelets per microliter. There are limited FDA approved treatments (i.e., corticosteroids, immunoglobulins) or surgical therapy (removal of the spleen) for adult patients with chronic immune thrombocytopenic purpura (ITP). ITP has historically been considered a disease of platelet destruction by the patient's own immune system. However, recent data also suggest that the body's natural platelet production processes are unable to compensate for low levels of platelets in the blood.

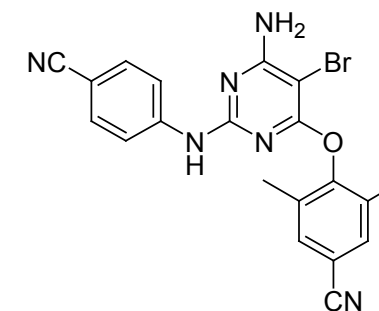
Romiplostim was designated an orphan drug by the FDA in 2003, as the chronic immune (idiopathic) thrombocytopenic purpura (ITP) population in the USA is thought to be around 60,000, with women outnumbering men by a factor of two. Due to the potential for serious side-effects, romiplostim will only be available through a restricted use program known as Network of Experts Understanding and Supporting (NEXUS). The network was developed as part of a risk evaluation and mitigation strategy that will also provide patient support and education and assist with safety data collection. Nplate is only dosed at 1 mcg/kg once weekly as a subcutaneous injection. However, the patient needs to discontinue the Nplate if the platelet count does not increase after 4 weeks at the maximum dose.

Name: Etravirine (Intelence)⁴
 Company: Tibotec
 Approval Date: Jan 2008
 Indication: HIV

Etravirine, a non-nucleoside reverse transcriptase inhibitor (NNRTI) for HIV infection, received approval from FDA in January 2008 for the use for patients with established resistance to other HIV drugs, making it the 30th anti-HIV drug approved in the United States. Unlike the currently available agents in the class, resistance to other NNRTIs does not seem to confer resistance to etravirine. Etravirine is marketed by Tibotec, a subsidiary of Johnson & Johnson.

Etravirine is administered 200 mg twice daily, which is not as convenient as efavirenz. It has been confirmed that the presence of the most common NNRTI mutation, K103N, did not affect the treatment response in the individuals on etravirine in the DUET studies. The presence at baseline of V179D, V179F, V179T, Y181V, or G190S was associated with a decreased virologic response to etravirine. In addition, the presence at baseline of three or more NNRTI mutations, as defined by the 2007 IAS-USA guidelines (V90I, A98G, L100I, K101E/P, K103N, V106A/I/M, V108I, V179D/F,

Y181C/I/V, Y188C/H/L, G190A/S, P225H) resulted in a decreased virologic response to etravirine. Cross-resistance to delavirdine, efavirenz, and/or nevirapine is expected after virologic failure with an etravirine-containing regimen. In addition, it is apparent that the more non-nucleoside mutations one has, the less likely etravirine is to work.



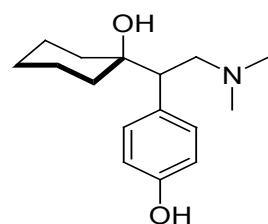
Name: Desvenlafaxine (Pristiq)⁵
 Company: Wyeth
 Approval Date: Feb 2008
 Indication: Major depressive disorder

Desvenlafaxine succinate, marketed under the name Pristiq, is an antidepressant of the serotonin-norepinephrine reuptake inhibitor (SNRI) class from Wyeth. It is a metabolite of venlafaxine (Effexor). Effexor, discovered and developed by Wyeth, was the first SNRI approved by the FDA for major depressive disorder (MDD) and is currently the most widely prescribed antidepressant in the world. Pristiq delivers the major active metabolite of Effexor in its active state without going through the CYP2D6 metabolic pathway. This could be beneficial when Pristiq is administered with other commonly prescribed medications metabolized through that pathway. Clinically, Pristiq has been dosed 50-400 mg/kg for efficacy. It has been shown that greater than 50 mg/kg has no additional effects but only increase adverse events and discontinuations.

MDD is a common mental disorder and a serious medical condition, affecting about 121 million people worldwide. In the United States, MDD affects approximately 15 million adults, or 6.7 percent of the U.S. population age 18 and older in a given year. Criteria for MDD include five or more of the following symptoms that have been present for at least two weeks, like depressed mood; loss of interest or pleasure; changes in appetite or weight; changes in sleeping patterns; psychomotor agitation or retardation; fatigue or low energy; feeling worthless or guilty for no reason; difficulty thinking or concentrating; or thoughts of death or suicide. Further

more, people with MDD must experience clinically significant distress or impairment in social, occupational or other important areas of functioning. For MDD, there is no single, gold standard of treatment. Some common first line pharmacological agents include SSRI, TCAs, DNRI, SNRI.

The most commonly observed adverse reactions in Pristiq-treated MDD patients in short-term fixed-dose studies (incidence $\geq 5\%$ and at least twice the rate of placebo in the 50 or 100 mg dose groups) were nausea, dizziness, insomnia, hyperhidrosis, constipation, somnolence, decreased appetite, anxiety, and specific male sexual function disorders. These side effect patterns are consistent with other SNRIs venlafaxine and Cymbalta. Relative rates are not available, as there were no head to head studies.

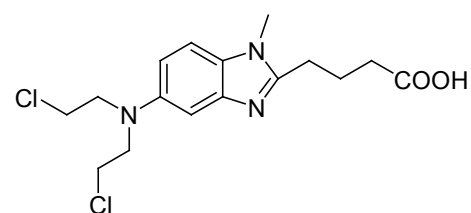


Name: Bendamustin hydrochloride (Treanda)⁶
Company: Cephalon
Approval Date: Mar 2008
Indication: Chronic lymphocytic leukaemia

Bendamustine (Treanda) is a nitrogen mustard used in the treatment of chronic lymphocytic leukemia (CLL) and non-Hodgkin's lymphoma (NHL). It belongs to the family of drugs called alkylating agents. Bendamustine received its first marketing approval in Germany, which is marketed under the trade name Ribomustin, by Astellas Pharma GmbH's licensee. The drug is indicated as a single-agent or in combination with other anti-cancer agents for indolent NHL, multiple myeloma. The drug can be injected intravenously 100 mg/m² on days 1 and 2 of a 28-day cycle, up to 6 cycles. Dose modifications need dependent hematologic toxicity or non-hematologic toxicity.

Treanda is a novel treatment with a unique chemical structure that is synthesized to combine an alkylating group and a purine-like benzimidazole component. Though the exact mechanism of action of treatment remains unknown, Treanda may act in two distinct ways

to kill cancer cells. Preclinical studies suggest that Treanda may lead to cell death by apoptosis as well as by an alternate cell death pathway as mitotic catastrophe. In March, 2008, Cephalon received approval from the FDA to market bendamustine in the US, where it is sold under the trade name Treanda. Bendamustine is the first drug approved for patients with chronic lymphocytic leukaemia (CLL) in the US since 2001.

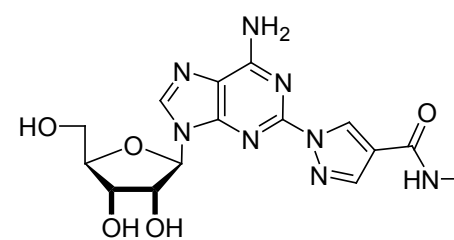


Name: Regadenoson (Lexiscan)⁷
Company: CV Therapeutics
Approval Date: Apr 2008
Indication: Pharmacological stress agent for radionuclide imaging

Regadenoson (Lexiscan) is an A_{2A} adenosine receptor agonist. This is a coronary vasodilator and is approved for use as a pharmacologic stress agent in radionuclide MPI studies in patients unable to undergo adequate exercise stress. It produces maximal hyperemia quickly and maintains it for an optimal duration that is practical for radionuclide myocardial perfusion imaging.

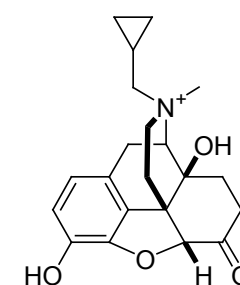
MPI tests (cardiac stress tests), commonly called cardiac stress tests, identify areas of poor blood flow in the heart that help detect and characterize coronary artery disease which is the most common type of heart disease. Many patients exercise on a treadmill to generate the increase in coronary blood flow necessary to perform an MPI study. However, almost half of the patients undergoing the 7.5 to 9.3 million cardiac stress tests each year are unable to exercise adequately because of medical conditions. For these patients, a pharmacologic stress agent that temporarily increases blood flow through the coronary arteries is used to mimic the increase in coronary blood flow caused by exercise.

Regadenoson has a 2-3 minute biological half-life, as compared with adenosine's 30 second half life. Regadenoson stress protocols use a single bolus, obviating the need for an intravenous line. Regadenoson stress tests are not affected by the presence of beta blockers.



Name: Methylnaltrexone bromide (Relistor)⁸
Company: Progenics
Approval Date: Apr 2008
Indication: Opioid-induced constipation

Each year, more than 1.5 million Americans receive palliative care due to an advanced illness, such as incurable cancer, end-stage heart, lung disease or AIDS. Many of these patients are prescribed opioids to manage their pain, but debilitating constipation is a major side effect. Opioids provide pain relief by specifically interacting with mu-opioid receptors within the central nervous system (CNS). However, opioids also interact with mu-opioid receptors found outside the CNS, such as those within the gastrointestinal tract, resulting in debilitating constipation. Side effects associated with opioids can be severe enough to limit pain management. Methylnaltrexone (Relistor) is one of the newer agents of peripherally-acting mu-opioid antagonists that act to reverse some of the side effects of opioid drugs such as constipation without affecting analgesia or precipitating withdrawals. Because it contains a permanently charged tetravalent nitrogen atom, it cannot cross the blood-brain barrier. Its antagonist effects throughout the body without opioid effects in the brain such as analgesia.

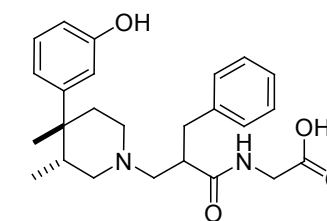


Name: Alvimopan (Entereg)⁹
Company: Adolor
Approval Date: May 2008
Indication: To accelerate gastrointestinal recovery following bowel resection surgery

Following major abdominal surgery, some patients develop a condition known as postoperative ileus (POI). POI is a disorder that causes temporary impairment of the gastrointestinal (GI) tract's motility, or the ability of the intestines to push out waste products (not a complete blockage of the GI tract), following surgery. POI can be a by-product of a patient taking opioid pain relievers, like morphine, prescribed after surgery which can slow or inhibit normal motility. Alvimopan works by blocking opioid effects in the bowel.

Alvimopan competitively binds to mu-opioid receptor in the gastrointestinal tract. Unlike methylnaltrexone that bears a quaternary amine, alvimopan owes its selectivity for peripheral receptors to its kinetics. Alvimopan binds to peripheral mu-receptors with a K_i of 0.2 ng/mL and dissociates slower than most other ligands. The potency and bioavailability of compounds allowed the dose to 12 mg 30 minutes to 5 hours prior to surgery followed twice 12 mg daily for up to 7 days.

Alvimopan is indicated in patients to avoid POI. Alvimopan accelerates the gastrointestinal recovery period as defined by the time to first bowel movement or flatus. The safety and efficacy of Entereg in post-operative patients were demonstrated in five studies that included 2,177 patients, of whom 1,096 received Entereg and 1,081 received placebo. Bowel recovery times ranged from 10 to 26 hours shorter for Entereg-treated patients compared to placebo-treated patients in the five studies. The most common side effects reported were low blood calcium levels, anemia and gastrointestinal problems, including constipation, dyspepsia (heartburn) and flatulence (excess bowel gas).

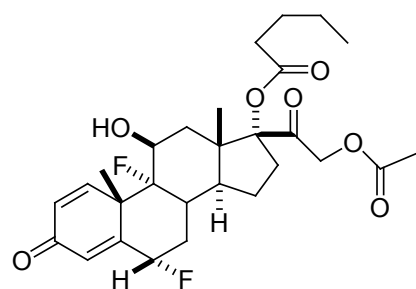


Name: Defluprednate (Durezol)¹⁰
Company: Sirion
Approval Date: Jun 2008
Indication: Inflammation and pain associated with ocular surgery

Defluprednate is a corticosteroid, a derivative of prednisolone obtained by fluorination at the 6- and 9-positions, followed by esterification of the 17 and 21-hydroxyl groups with butyric acid and acetic acid, respectively. Durezol, is a potent topical steroid that works rapidly

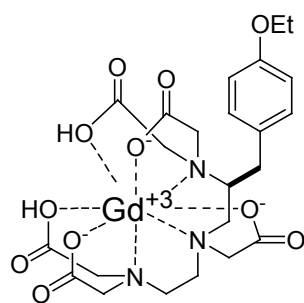
and effectively to resolve postoperative inflammation and pain.

Rapid resolution of inflammation and pain is very important following ocular surgery. Two Phase 3 trials were conducted to evaluate Durezol in patients diagnosed with significant postoperative inflammation (more than 10 anterior chamber cells). Durezol rapidly reduced inflammation and pain. Mean intraocular pressure (IOP) for all study groups remained within the normal range throughout the study. In these Phase 3 studies, patients were dosed for the first time after the ocular trauma from surgery had occurred. The results from these studies, particularly the ability to eliminate postoperative pain demonstrate that Durezol is a powerful option for postoperative care.



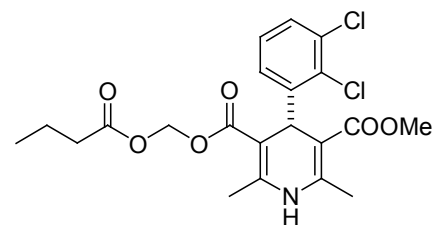
Name: Gadoxetate disodium (Eovist)¹¹
Company: Bayer
Approval Date: Jul 2008
Indication: Gadolinium-based contrast agent

Commonly a medical contrast medium is used to enhance the contrast of structures or fluids within the body in medical imaging. It is often used to enhance the visibility of blood vessels and the gastrointestinal tract. Arterial and portal venous MR images obtained with Gadoxetate disodium are comparable to those of computerized tomography (CT). Gadoxetate disodium has some protein binding that increases the plasticity of arterial and portal venous. Therefore a reduced amount of gadolinium intake compared with Magnevist when Magnevist is needed for imaging. Eovist has similar imaging properties as Magnevist and Omniscan. Eovist is excreted via the bile as well as via kidney.



Name: Clevidipine butyrate (Cleviprex)¹²
Company: Medincines
Approval Date: Aug 2008
Indication: Peri-operative hypertension when oral therapy is not feasible or not desirable

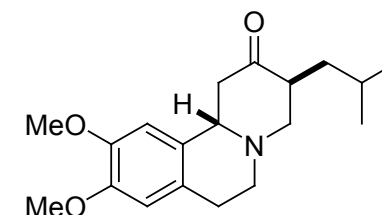
Intravenous acute severe antihypertensive agents are used in clinical situations in which the immediate, precise control of blood pressure is a clinical necessity. Clevidipine is a new, vascular-selective and an ultra short-acting dihydropyridine calcium channel blocker, which exerts its hemodynamic effects through selective arterial vasodilation without effecting the venous circulation. Because it is a potent coronary vasodilator, reduction in mean arterial pressure does not impair coronary perfusion. The unique properties of clevidipine include an ultra-short pharmacodynamic duration of action and a half-life after intravenous administration of approximately 2 min. The ultra-short effects result in very rapid onset and offset of antihypertensive effects. Cleviprex is intended for intravenous use. The desired therapeutic response for most patients occurs at doses of 4-6 mg/hour. In clinical trials performed in patients undergoing cardiac surgery, clevidipine proved superior to nitroprusside and nitroglycerin in maintaining blood pressure within predetermined ranges during the perioperative period. Its safety profile is comparable to nicardipine and nitroglycerin. Clevidipine constitutes a useful addition to available intravenous agents and could prove particularly valuable in circumstances that require the ability to rapidly terminate the blood pressure-lowering effects of administered agents.



Name: Tetrabenazine (Xenazine)¹³
Company: Prestwick
Approval Date: Aug 2008
Indication: Chorea associated with Huntington's disease

Tourette syndrome (TS) is characterized by multiple motor tics plus one or more vocal (phonic) tics, which characteristically wax and wane. It can no longer be considered the rare and bizarre syndrome that it was once thought to be. The concepts surrounding TS is now recognized to be associated with a wide variety of behaviors and psychopathologies. It is suggested that TS is heterogeneous from a variety of standpoints including clinical presentation and psychopathology, and thus neuropharmacological responses and possibly even aetiological and genetic mechanisms.

Tetrabenazine is a drug for the symptomatic treatment of hyperkinetic movement disorder and is available in the US as an orphan drug. In August 2008, the FDA approved the use of tetrabenazine to treat chorea associated with Huntington's disease (HD), the first in the US. The compound has been known since the 1950s. Unlike many of the antipsychotics, tetrabenazine is not known to cause tardive dyskinesia, and in fact can be an effective treatment for the antipsychotic-induced movement disorder. Tetrabenazine reversibly inhibits the human vesicular monoamine transporter type 2 ($k_i = 100\text{nM}$). One interesting aspect of the drug dosed at 50 mg is that it has a QTc prolongation for 8 msec mean increases. QTc prolongation effects at higher exposures to either tetrabenazine or its metabolites have not been evaluated.

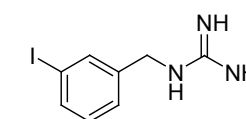


Name: Iobenguane I-123 (AdreView)¹⁴
Company: GE Healthcare
Approval Date: Sep 2008
Indication: Radiopharmaceutical agent for the detection of primary or metastatic pheochromocytoma or neuroblastoma

Iobenguane or meta-iodobenzylguanidine (mIBG) is a physiological analog of the guanidines, such as guanethidine and phenethylguanidine. In adrenergic nerves, guanidines are believed to share the same transport pathway as norepinephrine. Guanidines accumulate in and displace norepinephrine from intraneuronal storage granules. Similarly, ¹²³I- and ¹³¹I-mIBG are concentrated, stored in, and released from chromaffin granules. The retention of ¹²³I- and ¹³¹I-mIBG in the adrenal medulla may be a result of their uptake in adrenergic neurons and subsequent sequestration into chromaffin storage granules. Due to their selective uptake mechanism, ¹²³I- and ¹³¹I-mIBG allow specific detection and localization of neuroendocrine tumors and adrenal medullary hyperplasia. The gamma emissions given off by ¹²³I- and ¹³¹I-mIBG allow detection of adrenergic tumors by scintigraphy.

FDA approved ¹²³I-iobenguane injection (AdreView) for use in the detection of primary or metastatic pheochromocytoma or neuroblastoma as an adjunct to other diagnostic tests. Iobenguane accumulates in adrenergically innervated tissues as well as tumors derived from the neural crest. The uptake in normal adrenal glands is very low. However, hyperplastic adrenals and tumors such as pheochromocytoma, neuroblastoma, and other tumors with neurosecretory granules have a relatively higher uptake. The uptake of ¹²³I-iobenguane injection by metabolically active pheochromocytoma or neuroblastoma allows scintigraphic visualization of these tumors.

After intravenous administration, there is rapid uptake of mIBG mainly in the liver, and in lesser amounts in the lungs, heart, spleen, and salivary glands.

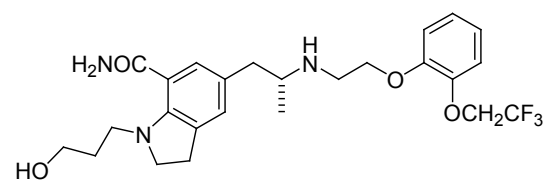


Name: Silodosin (Rapaflo)¹⁵
Company: Watson
Approval Date: Oct 2008
Indication: Benign Prostatic hyperplasia

BPH (Benign Prostatic Hypertrophy) is a condition found only in men and is characterized by a non-cancerous enlargement of the prostate gland. Symptoms of BPH include urinary difficulty, urinary frequency and an inability to complete bladder emptying. The number of BPH patients has been increasing with the expansion of the elderly population. In the United States, BPH affects more than half of men in their 60's and as many

as 90 percent of men by the age of 85. According to IMS data, BPH symptoms were the primary reason patients visited their urologists in 2006.

Blocking these receptors relaxes the smooth muscles, resulting in an improvement in urine flow and a reduction in BPH symptoms. The selective binding of silodosin to the alpha (1A) receptors is substantially greater than the binding to the cardiovascular-associated alpha (1B) receptors and thereby maximizes target organ activity while minimizing the potential for blood pressure effects. Silodosin is 97% protein bound, has a large volume distribution (49.5 L) and has a moderate bioavailability of 32% that enable the drug to be dosed at 8 mg daily to treat BPH.



Name: Lacosamide (Vimpat)¹⁶
Company: Schwarz
Approval Date: Oct 2008
Indication: Partial-onset seizures in epilepsy

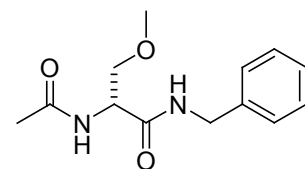
Epilepsy is a chronic neurological disorder affecting approximately three million people in the U.S. Less than half (47%) will attain seizure control with their first antiepileptic drug (AED), and more than 30% will continue to experience seizures despite trying two or more AEDs.

Lacosamide acts by enhancing slow inactivation of voltage gated sodium channels. Voltage gated sodium channels are the membrane proteins responsible for generating the neuronal action potential, the all or none electrical event which causes neurons to release neurotransmitter. During an action potential voltage gated sodium channels undergo fast inactivation, a process which takes a few milliseconds. This inactivation prevents the channel from opening and helps end the action potential. Many typical antiepileptic drugs, like carbamazepine or lamotrigine, slow the recovery from inactivation and hence reduce the ability of neurons to fire action potentials. Inactivation occurs only in neurons firing action potentials. This means that drug that modulate fast inactivation selectively reduce the firing in active cells.

Slow inactivation is a similar process, except that it does

not produce complete blockade of voltage gated sodium channels, and it occurs over the course of hundreds of milliseconds or more, and recovery from this state takes equally as long. Lacosamide makes this inactivation happen at less depolarized membrane potentials. This means that lacosamide only effects neurons which are depolarized or active for long periods of time, typical of neurons at the focus of an epileptic focus.

Lacosamide does not affect AMPA, kainate, NMDA, GABA_A, GABA_B or a variety of dopaminergic, serotonergic, adrenergic, muscarinic or cannabinoid receptors and does not block potassium or calcium currents. The patients need to take 50 mg twice daily for their epilepsy. The dose can be expanded up to 400 mg dependent on efficacy and tolerability. Having a new antiepileptic drug option may offer adults with partial onset seizures the chance to obtain seizure control.

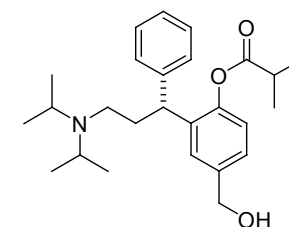


Name: Fesoterodine fumarate (Toviaz)¹⁷
Company: Pfizer
Approval Date: Oct 2008
Indication: Overactive bladder disorder

Symptoms of overactive bladder (OAB) can have a profound effect on workplace productivity, social and sexual activity and sleep. Overactive bladder may also lead to other health problems, such as falls and fractures, urinary tract infections, skin disorders, sleep problems, and depression. Despite the significant impact of OAB on patients' lives, research concludes that the embarrassment and stigma associated with incontinence can cause sufferers to try to hide the condition from families, friends and even their doctors. As a result, many with incontinence conditions suffer without seeking help. Overactive bladder is a treatable medical condition defined by urinary urgency (a sudden compelling desire to pass urine that is difficult to defer) with or without urgency urinary incontinence, increased daytime urinary frequency and nocturia.

Fesoterodine (Toviaz) is an antimuscarinic drug developed by Schwarz Pharma AG to treat overactive bladder syndrome. Fesoterodine is a prodrug. It is broken down into its active metabolite, 5-hydroxymethyl tolterodine, by plasma esterases. New once-daily Toviaz can significantly reduce the number of urge urinary incontinence episodes

and the frequency of urination over 24 hours. The two efficacious and well-tolerated doses of Toviaz, 4 mg and 8 mg, allow dosing flexibility to optimize treatment based on individual patient response and tolerability.

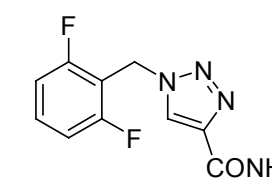


Name: Rufinamide (Banzel)¹⁸
Company: Eisai
Approval Date: Nov 2008
Indication: Seizures associated with Lennox-Gastaut syndrome

Lennox-Gastaut syndrome is a severe form of epilepsy that usually begins before 4 years of age, and can be caused by brain malformations, severe head injury, central nervous system infection and inherited degenerative or metabolic conditions. In 30-35 percent of cases, no cause can be found. Patients may have periods of frequent seizures mixed with brief, relatively seizure-free periods; and suffer from varying types of seizures including tonic (stiffening of the body, upward deviation of the eyes, dilation of the pupils, and altered respiratory patterns), atonic (brief loss of muscle tone and consciousness, causing abrupt falls), atypical absence (staring spells), and myoclonic (sudden muscle jerks). Most children with Lennox-Gastaut syndrome experience some degree of impaired intellectual functioning or information processing, along with developmental delays and behavioral disturbances.

Rufinamide, a novel triazole derivative structure, is an anticonvulsant medication. The precise mechanism(s) by which exerts its antiepileptic effect is unknown. The suspected mechanism of action is limitation of sodium-dependent action potentials, thought to result in a membrane stabilizing effect. The absorption rate with drug is at least 85% with 600 mg of oral dose under fed conditions.

Rufinamide was approved by the FDA in November 2008 for the adjunctive treatment for the seizures associated with Lennox-Gastaut Syndrome and as adjunctive treatment for partial-onset seizures.

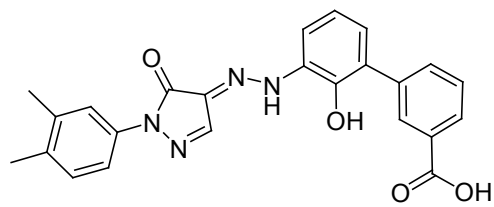


Name: Eltrombopag (Promacta)¹⁹
Company: GlaxoSmithKline
Approval Date: Nov 2008
Indication: Thrombocytopenia in patients with chronic immune (idiopathic) thrombocytopenic purpura

Eltrombopag is an oral, non-peptide thrombopoietin receptor agonist that has been shown in pre-clinical research and clinical trials to stimulate the proliferation and differentiation of megakaryocytes, the bone marrow cells that give rise to blood platelets. Eltrombopag was discovered as a result of a research collaboration between GlaxoSmithKline and Ligand Pharmaceuticals. It was developed by GlaxoSmithKline.

Eltrombopag is a medication developed for conditions that lead to thrombocytopenia (abnormally low platelet counts). It is a small molecule agonist of the c-mpl (TpoR) receptor, which is the physiological target of the hormone thrombopoietin. It was designated as an orphan drug in the USA and European Union.

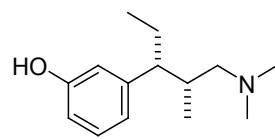
In preclinical studies, the compound was shown to interact selectively with the thrombopoietin receptor, leading to activation of the JAK-STAT signaling pathway and increased proliferation and differentiation of megakaryocytes. Eltrombopag is for the treatment of thrombocytopenia in patients with chronic immune (idiopathic) thrombocytopenic purpura (ITP) who have an insufficient response to corticosteroids, immunoglobulins or splenectomy. Preventing platelet destruction has always been the primary means of treating patients with ITP. Recent advances, like the clinical trials of eltrombopag, show that increasing the production of platelets may also play a significant role in treating this disorder. Eltrombopag is the first oral thrombopoietin (TPO) receptor agonist approved for adult patients with chronic ITP. A starting dose of 50 mg is needed for most patients. For patients of East Asian ancestry or patients with moderate or severe hepatic insufficiency, the starting dose is 25 mg once daily.



Name: Tapentadol hydrochloride (Nucynta)²⁰
 Company: Ortho-McNeil-Janssen
 Approval Date: Nov 2008
 Indication: Moderate to severe acute pain

Tapentadol is a centrally-acting analgesic with a unique dual mode of action as an agonist at the mu-opioid receptor and as a norepinephrine reuptake inhibitor. It is considered to have potency between morphine and tramadol. Respiratory depression is a possible adverse event of tapentadol. These drugs modify sensory and affective aspects of pain, inhibit the transmission of pain at the spinal cord and affect activity at parts of the brain that control how pain is perceived. Norepinephrine reuptake inhibitors increase the level of norepinephrine in the brain by inhibiting its re-absorption into nerve cells; these compounds have analgesic properties. Patients receiving other mu-opioid agonist analgesics, general anesthetics, phenothiazines, other tranquilizers, sedatives, hypnotics, or other CNS depressants (including alcohol, opioids or illicit drugs) concomitantly with tapentadol may exhibit an additive CNS depression. Interactive effects resulting in respiratory depression, hypotension, profound sedation, or coma may result if these drugs are taken in combination with tapentadol.

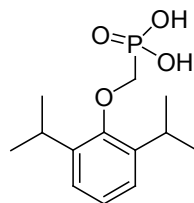
Tapentadol can be abused in a manner similar to other mu-opioid agonists. Tapentadol may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery. Tapentadol should be prescribed with care in patients with a history of a seizure disorder or any condition that would put the patient at risk of seizures. The company must wait for a drug scheduling decision from the United States Drug Enforcement Administration before it can make tapentadol available for sale.



Name: Fospropofol disodium (Lusedra)²¹
 Company: Eisai
 Approval Date: Dec 2008
 Indication: Monitored anaesthesia care sedation

Fospropofol (Lusedra) is a sedative/anesthetic drug. As a water-soluble prodrug of the popular sedative/hypnotic/anesthetic drug propofol, fospropofol is metabolized into propofol by the liver.

Fospropofol, 6.5mg/kg followed by supplemental dose of 1.6 mg/kg injection is intended to eliminate the disadvantages associated with the current lipid emulsion formulation of propofol by delivering propofol as a water-stable phosphono-O-methyl prodrug. Fospropofol injection possesses a unique and distinct pharmacokinetic and pharmacodynamic profile. Compared with propofol emulsion, Lusedra is associated with a slightly longer time to peak effect and a more prolonged pharmacodynamic effect. These traits can be desirable for endoscopic procedures such as upper GI endoscopy, colonoscopy, bronchoscopy, as well as for some surgical procedures done under local or regional anesthesia. The other advantage of fospropofol is that, being water-soluble, the problems associated with lipid formulated propofol (e.g., pain at the IV catheter site, potential for hyperlipidemia with long-term administration, and an increased chance for bacteremia) are expected to be less frequent. Fospropofol is hydrolyzed to propofol liberated as an active metabolite together with formaldehyde and phosphate.



Name: Plerixafor (Mozobil)²²
 Company: Genzyme
 Approval Date: Dec 2008
 Indication: Autologous transplantation in patients with non-Hodgkin's lymphoma and multiple myeloma

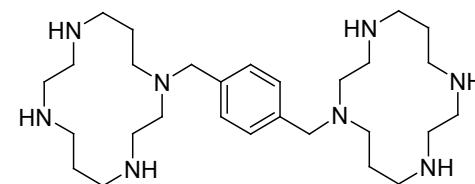
Plerixafor (Mozobil) is a macrocyclic compound and potential fusion inhibitor. It is an antagonist (more accurately a par-

tial agonist) of the chemokine receptor CXCR4. The CXCR4 chemokine receptor and its ligand SDF-1 are important in hematopoietic stem cell homing to the bone marrow and in hematopoietic stem cell quiescence. Plerixafor has been found to be a strong inducer of "mobilization" of hematopoietic stem cells from the bone marrow to the bloodstream as peripheral blood stem cells.

Peripheral blood stem cell mobilization, which has become extremely important as a source of hematopoietic stem cells for transplantation over the past 10 to 15 years, is generally performed using the cytokine drug G-CSF, but is ineffective in around 15 to 20% of patients. Plerixafor offers clinical promise as a drug for peripheral blood stem cell mobilization.

Plerixafor has orphan drug status in the United States for the mobilization of hematopoietic stem cells. This procedure is already well known and has been practiced extensively in trials to boost blood stem cell production in patients undergoing treatment for various forms of lymphoma. It boosts blood stem cell production so that enough can be saved and transplanted back into the patient once their cancer, which destroys blood cells, has been eradicated.

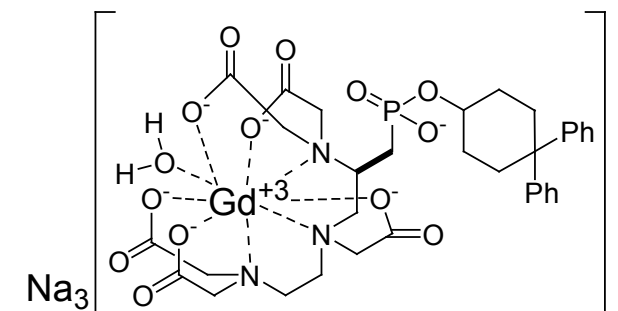
However, the real breakthrough of the work was to show that by giving a different combination - Mozobil preceded by vascular endothelial growth factor (VEGF) - they could boost levels of two other types of stem cell. Mesenchymal stem cells (MSCs) promote regeneration of bone and tissue, and so could be used for bone repair. They also damp down inflammation, and could be used to treat conditions such as rheumatoid arthritis. Epithelial progenitor cells (EPCs), meanwhile, stimulate the growth and repair of blood vessels, and could prove useful in restoring blood flow to the heart or brain following heart attacks or strokes. The drug can be subcutaneous injected based on 0.24 mg/kg actual body weight 11 hours prior to initiation of apheresis.



Name: Gadofosveset (Vasovist)²³
 Company: Epix
 Approval Date: Dec 2008
 Indication: Gadolinium-based contrast agent

Vasovist is an injectable intravascular contrast agent designed to provide improved imaging of the vascular system through magnetic resonance angiography imaging (MRA). Vasovist is the first contrast agent approved for marketing in the United States for use with MRA, a non-invasive modality for imaging blood vessels. In 2007, there were approximately 1.3 million MRA procedures performed in the United States using contrast agents not specifically approved for this procedure. MRA is a less invasive procedure than x-ray angiography, allowing for reduced patient discomfort and recuperation time.

Vasovist is a first-in-class contrast agent offers good resolution angiography, a high signal per dose, a long imaging window timeframe and single-dose imaging of multiple vessel beds. The resulting high-quality image will allow physicians to fully utilize MRA as a meaningful diagnostic and therapeutic tool. In addition, the albumin-binding properties of Vasovist make it ideal for vascular imaging as opposed to other gadolinium agents that are rapidly cleared from the blood stream and have a narrow imaging window.



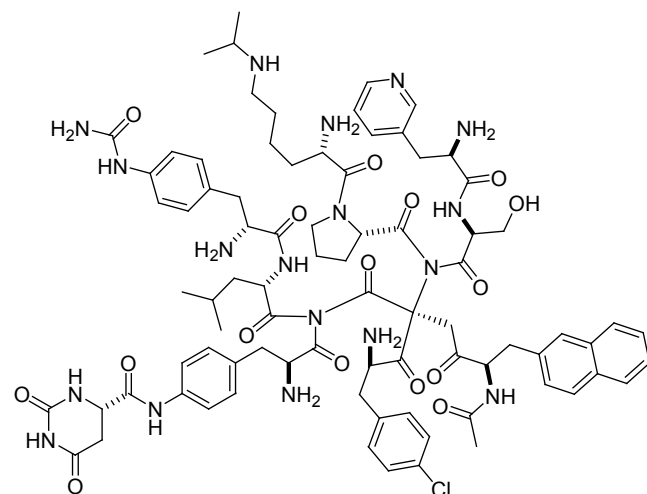
Name: Degarelix (Firmagon)²⁴
 Company: Ferring
 Approval Date: Dec 2008
 Indication: Advanced prostate cancer

Degarelix (Firmagon) is a subcutaneous injectable gonadotropin-releasing hormone antagonist (GnRH antagonist). It has an immediate onset of action, suppressing gonadotropins, testosterone, and prostate-specific antigen (PSA) in prostate cancer. Use of a GnRH receptor antagonist is a highly efficient way to stop the production of testosterone. Prostate cancer can be treated with immediate inhibition of the GnRH receptors, inducing rapid reduction of testosterone to castrate levels, and sustaining those levels over time, which are the goals of systemic therapy. Prostate cancer is known to grow in the presence of testosterone. Suppression of testosterone has been a treatment goal for advanced

prostate cancer for many years. Surgical castration was the standard method of reducing testosterone from the 1940s until the mid-1980s when the earliest forms of medical castration, luteinizing hormone releasing hormone (LHRH) agonists, were introduced.

Degarelix is the only GnRH receptor antagonist approved by the FDA for the treatment of hormonally-sensitive advanced prostate cancer. The drug is given 240 mg as two injections of 120 mg each. Degarelix achieves medical castration differently than LHRH agonists, specifically by binding reversibly to GnRH receptors on cells in the pituitary gland, quickly reducing the release of gonadotropins and consequently testosterone. The drug was maintained of 80 mg administered as a single injection every 28 days.

In the clinical trial, PSA levels were also monitored as a secondary endpoint. PSA levels were lowered by 64% two weeks after administration of degarelix, 85% after one month, 95% after three months, and remained suppressed throughout the one year of treatment. These PSA results should be interpreted with caution because of the heterogeneity of the patient population studied. No evidence has shown that the rapidity of PSA decline is related to a clinical benefit.



Endnotes

1. <http://www.fda.gov/cder/foi/label/2008/125249lbl.pdf>
2. <http://www.fda.gov/cder/foi/label/2008/125160s000lbl.pdf>
3. <http://www.fda.gov/cder/foi/label/2008/125268lbl.pdf>
4. <http://www.fda.gov/cder/foi/>

5. <http://www.fda.gov/cder/foi/label/2008/022187lbl.pdf>
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23. <http://www.fda.gov/cder/foi/label/2008/022311lbl.pdf>
24. <http://www.fda.gov/bbs/topics/NEWS/2008/NEW01934.html>
25. <http://www.fda.gov/cder/foi/label/2008/022201lbl.pdf>

Innovative Prescription Medicines Support the Goals of Chinese Healthcare Reform

Helen Chen



About the Authors: Ms. Helen Chen is a partner at L.E.K. Consulting based in Shanghai and head of L.E.K.'s China life sciences practice. She has 20 years of life science industry and consulting experience in United States and Asia, and has been practicing in China since 2000. Helen's practice advises life sciences companies in all stages of growth, and financial investors in the commercial opportunities in the China life science sector. Helen was previously associate director of finance at Genentech in San Francisco, California, and held sales planning roles at Abbott Laboratories in North Chicago, Illinois. Helen has an honors BA from Harvard University in applied mathematics and attended the Kellogg Graduate School of Management at Northwestern University. She was a member of Board of Directors for U.S. Pharmaceutical Management Sciences Association (PMSA) from 1995 to 1997, and was honored by Who's Who Among American Women from 1993 to 1995.

Introduction

The Chinese government is committed to a multi-year healthcare reform "to establish a healthcare system covering urban and rural residents, and to provide safe, effective, convenient, and affordable medical service." This was stated by President Hu Jintao at the 17th China Communist Party Congress in 2007 and then emphasized again a year later in the draft plan for healthcare reform released in October 2008.

In this discussion, while healthcare costs and drug prices are featured prominently, the quality of medicine and the optimal use of medicine, whether innovative or generic, seem to have been neglected. Pharmaceuticals is an essential and valuable component of any healthcare system and often the most cost effective therapy to manage a disease.

This paper highlights key challenges facing China in optimal use of medicines and suggests that in order to realize the value from medicines and to achieve the government's stated goal of providing "safe, effective, convenient, and affordable" medical service to Chinese patients, optimal use of high quality medicines has to be assured. It concludes with recommendations on public policy actions that can be taken to make progress toward achieving this goal.

Challenges in the Optimal Use of Medicines in China

The World Health Organization (WHO) defines optimal use of medicine as "patients receive[ing] medications appropriate to their clinical needs, in doses that meet their own individual requirements, for an adequate period of time, and at the lowest cost to them and their community"¹. R&D-based companies devote enormous effort to discover optimal treatment therapies and promote high quality standards.

Despite the benefits of optimal use of medicines, misuse and irrational use of medicine are problems worldwide. According to the WHO, over half of all medicines are prescribed, dispensed or sold inappropriately, and half of all patients fail to take them correctly². China is no exception, and faces some specific challenges.

Inconsistent medicine quality

WHO estimates that 10% of drugs sold worldwide are counterfeit or substandard (often with little or no active pharmaceutical ingredient); this figure runs to 30% in poorer countries, especially in Southeast Asia³. In China, high incidence of counterfeit and substandard medicines undermine treatment and pose a potential risk to patient health, as in 2008 when quality problems of human immunoglobulin and TCM injections caused many deaths⁴.

Severe price competition among the large number of pharmaceutical manufacturers in China led many to cut corners on quality standards⁵.