Milestones:

Aspirin™: The road to success

- **400 BC**: Hippocrates uses willow bark to reduce fever and pain.
- **1897**: In a Bayer laboratory in Wuppertal, Germany, young scientist Dr. Felix Hoffmann is the first to succeed in synthesizing a chemically pure and stable form of acetylsalicylic acid (ASA), which becomes the active ingredient in Aspirin™.
- **1899**: Aspirin™ is registered as a trademark. It is launched on the market in powder form. Bayer delivers the medicine to pharmacies in small 250-gram glass vials. 500 mg of the powder is then weighed out and dispensed to customers in small paper bags. Just one year later, Bayer launches the analgesic in its classic tablet form – one of the first medicines to be marketed in this dosage form.
- **1900**: Bayer’s Aspirin™ is launched in Japan.
- **1901**: Aspirin™ is launched in Brazil.
- **1909**: After just ten years, Bayer is already generating some 30 percent of its global sales with Aspirin™ in the United States (US). The brand becomes one of the ten most frequently prescribed medicines in the USA.
- **1915**: Aspirin™ becomes available without a prescription and becomes a best-seller in the USA.
- **1918**: World War I briefly puts the company’s growth to a halt: The Treaty of Versailles forces Bayer to give up its patent in the USA. Everything, from money to the new Aspirin™ production plant is seized. Sterling Winthrop (then Sterling Drug) buys the US company at a US government auction for a total of 5.3 million dollars.
- **1924**: Advertising for Bayer’s Aspirin™ can be seen on vehicles all over the world.
- **1948**: Dr. Lawrence Craven, a California, US general practitioner, observes that the rate of heart attack is low in the several hundred patients for whom he has recommended acetylsalicylic acid. He publishes his findings in the Annals of Western Medicine & Surgery two years later, but his observations are initially ignored.
• **1949**: Aspirin™ turns 50, and the following year, is for the first time featured in the Guinness Book of Records as the most frequently sold pain reliever in the world.

• **1950**: The American Medical Association issues a statement supporting the safety and effectiveness of acetylsalicylic acid as a pain reliever.

• **1969**: A box of Bayer™ Aspirin flies to the moon aboard Apollo 11.

• **1971**: British pharmacologist Sir John R. Vane elucidates the mechanism of action of acetylsalicylic acid. He discovers acetylsalicylic acid has analgesic, antipyretic and anti-inflammatory effects because it inhibits the synthesis of prostaglandins in the body.\(^1\) In the same year, J.B. Smith and A.L. Willis produce the first evidence that the blood-thinning effect of acetylsalicylic acid is based on irreversible inhibition of prostaglandin production in blood platelets.\(^2\)

• **1971**: Aspirin™ plus C, an effervescent tablet is introduced to the market in Germany. In part because of its buffering additives, this drug is gentler to the stomach and acts faster.

• **1977**: A study reports that acetylsalicylic acid can prevent ischemic stroke in appropriate patients.\(^3\) In the same year, the World Health Organization (WHO) introduces its “Essential Drug List”. Aspirin™ is included right from the start as an essential analgesic.

• **1978**: The Canadian Cooperative Study is published in the “New England Journal of Medicine” showing that acetylsalicylic acid can markedly reduce the incidence of transitory ischemic attacks (TIA), stroke, or death.\(^4\)

• **1982**: British pharmacologist Professor John Vane receives the Noble Prize for Medicine for his discovery that the anti-inflammatory properties of acetylsalicylic acid result from its ability to inhibit the body’s production of certain chemical mediators (prostaglandins) that promote inflammation.

• **1983**: Publication of the Veterans Administration Cooperative Study (VACS) trial, one of the five key trials demonstrating that acetylsalicylic acid reduces the risk of events in patients with angina.\(^5\)

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• **1985**: The US Food and Drug Administration approves the use of acetylsalicylic acid under a doctor’s direction to prevent heart attack in patients who have had a previous heart attack or unstable angina, and to prevent recurrent stroke in men with previous transitory ischemic attacks.

• **1988**: Publication of the British Doctors’ Trial (BDT)\(^6\), which suggests the incidence of transitory ischemic attacks was significantly lower in patients regularly taking acetylsalicylic acid.

• **1988**: The Antiplatelet Trialists’ Collaboration publishes the results of a meta-analysis demonstrating that acetylsalicylic acid significantly reduces the risk for thromboembolic events.\(^7\) Also that year, the results of the Second International Study of Infarct Survival (ISIS-2) are published. According to the authors, acetylsalicylic acid reduces the risk of death if taken during a heart attack and for 30 days thereafter.\(^8\)

• **1989**: Publication of the Physicians’ Health Study (PHS),\(^9\) which demonstrated a clear reduction in first heart attack in healthy male subjects taking acetylsalicylic acid. PHS is stopped early due to the markedly lower death rate of those in the acetylsalicylic acid group versus the placebo group. Newsweek headlines the PHS story: “Aspirin breakthrough.”

• **1990**: The American Heart Association begins to recommend low-dose acetylsalicylic acid therapy to reduce risk of recurrent heart attack in patients with a history of this cardiovascular event.

• **1990–1992**: The Swedish RSIC (Risk of myocardial infarction and death during treatment with low dose acetylsalicylic acid and intravenous heparin in men with unstable coronary artery disease) trial is the first of five key trials demonstrating that low-dose acetylsalicylic acid may reduce the risk for heart attack in patients with unstable angina pectoris by at least 50 percent.\(^10\) This time period also sees publication of a trial by Ridker et al.\(^11\), and of the Swedish Angina Pectoris trial\(^12\), two other key trials.

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\(^{12}\) The Swedish Angina Pectoris Aspirin Trial (SAPAT) Group. Double-blind trial of aspirin in primary
demonstrating that acetylsalicylic acid reduces the risk of events in patients with angina.

- **1992:** Acetylsalicylic acid is listed as an essential drug for thrombosis prevention in the World Health Organization’s Essential Drug List. That same year, a chewable Aspirin™ tablet is introduced. It is buffered with calcium carbonate and thus suitable for patients with sensitive stomachs.

- **1993:** Bayer introduces, in Germany and other various countries, Aspirin™ Protect, a low-dose acetylsalicylic acid formulation for use by appropriate at-risk patients in the prevention of cardiovascular events.

- **1995:** Bayer buys the OTC (over the counter) division of Sterling Winthrop for 1 billion US dollar, regaining ownership of its medicine now marketed there as Bayer™ Aspirin. In Bitterfeld, Germany, one of the most sophisticated pharmaceutical production plants in Europe is opened.

- **1996:** Twice as many people choose acetylsalicylic acid over the personal computer as an invention they couldn’t live without, in a national survey on inventions conducted by the Michigan Institute of Technology (MIT).  

- **1997:** Acetylsalicylic acid, the active ingredient in Aspirin™, celebrates its centenary.

- **1997:** Results of the International Stroke Trial, with nearly 20,000 patients in 36 countries, are published. They support use of acetylsalicylic acid within 48 hours after ischemic stroke.

- **1998:** The Thrombosis Prevention Trial (TPT) and Hypertension Optimal Treatment (HOT) study are published. These are among the studies that pave the road for the approval of acetylsalicylic acid for primary prevention in more than 50 countries. A recommendation is published, based on the findings of TPT and HOT, by the second Joint Task Force of European and Other Societies on Coronary Prevention for low-dose acetylsalicylic acid therapy to be used for prevention of first myocardial infarct in individuals at high risk of cardiovascular disease.

- **1998:** The US Food and Drug Administration approves expanded cardiovascular professional labeling for acetylsalicylic acid use in secondary prevention. New indications now include use of acetylsalicylic acid as directed by a physician in: reducing the risk of death during a suspected heart attack; preventing a recurrent

13 The Lemelson-MIT Program. Lemelson-MIT Invention Index 1996.
ischemic stroke or transient ischemic attack (TIA) in men and women; reducing the risk of recurrent heart attack and ischemic stroke; preventing heart attack and death in patients with stable angina; for patients who have undergone revascularization procedures when there is a pre-existing condition for which acetylsalicylic acid is already indicated – coronary artery bypass graft (CABG), percutaneous transluminal coronary angioplasty (PTCA), carotid endarterectomy.

- **1998**: Aspirin™ Prevent is launched in Brazil.
- **1999**: Bayer Aspirin™ Cardio is launched in China. Aspirin is approved in China and Spain for use in secondary prevention.
- **1999**: On March 6, exactly 100 years after Aspirin™ was entered into the trademark register of the Imperial Patent Office in Berlin, Bayer set a Guinness world record by transforming its 122 meter tall headquarters building in Leverkusen into the largest Aspirin™ box. The building is wrapped with more than 22,500 square meters of fabric to celebrate the 100th birthday of Aspirin™.
- **1999**: Acetylsalicylic acid takes its place among such medical advances as the stethoscope and artificial heart when it is inducted into the Smithsonian Institution’s National Museum of American History, USA.
- **2001**: Bayaspirin™, for cardiovascular event prevention, is launched in Japan.
- **2003**: Aspirin™ Complex and Aspirin™ Effect are introduced in Germany.
- **2003**: Publication of the Primary Prevention Project (PPP) trial, one of the five key trials demonstrating that acetylsalicylic acid reduces the risk of events in patients with angina. The trial was stopped early because of positive trends for acetylsalicylic acid use identified from internal analyses, and newly available evidence from the Thrombosis Prevention Trial (TPT) and Hypertension Optimal Treatment (HOT) studies regarding the benefits of low-dose acetylsalicylic acid therapy in the prevention of cardiovascular events in appropriate high-risk patients.
- **2004**: British researcher Professor Derek W. Gilroy elucidates the anti-inflammatory properties of acetylsalicylic acid, adding to previous research on its mechanism of action by Sir John Vane and others.
- **2005**: Publication of the Women’s Health Study (WHS), a landmark 10-year randomized trial in 40,000 apparently healthy female subjects. In the trial, low-dose acetylsalicylic acid taken every other day is found to reduce all major CV events, including heart

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attack and ischemic stroke, in women 65 or older. In the total population of women studied – primarily healthy women between the ages of 45-55, the study finds a reduction in ischemic stroke but no significant benefit in preventing first heart attack or cardiovascular death.

- **2007**: Publication of the Critical Leg Ischaemia Prevention Study (CLIPS), one of relatively few trials at this time investigating the prevention of cardiovascular and cerebrovascular disease that have included patients with peripheral arterial disease (PAD). CLIPS suggests a beneficial effect of low-dose acetylsalicylic acid in the prevention of first vascular events in patients with PAD.

- **2009**: Publication of a meta-analysis from the Antithrombotic Trialists' Collaboration, using individual patient data from six prospective clinical studies, which finds statistically significant reductions with low-dose acetylsalicylic acid for serious vascular events, major coronary events, non-fatal heart attacks and ischemic stroke. Furthermore, their analyses demonstrated a greater than 2:1 positive benefit/risk ratio with low-dose acetylsalicylic acid.

- **2011**: Published meta-analysis, by Lanas et al, of patient level data in 67 mostly single-dose clinical trials reaffirms acetylsalicylic acid safety for use in pain relief. The analysis shows no drug-related serious gastrointestinal (GI) side effects or other complications associated with acetylsalicylic acid when used in apparently healthy, non-elderly populations without known risk of gastrointestinal complications.

- **2012**: Publication in the journal Headache by Lampl et al, which reaffirms the effectiveness of acetylsalicylic acid as a first-line treatment of migraine or episodic tension type headache and finds that pre-treatment headache intensity does not predict potential success or failure of acetylsalicylic acid.

- **2012**: Bayer’s global Aspirin™ business continues to exhibit significant sales performance and remains one of the company’s top ten brands. Today, Aspirin™ is one of the top three branded over the counter analgesics worldwide.

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2013: A meta-analysis, by Baron et al., of 78 clinical trials reaffirms acetylsalicylic acid safety for use in pain relief. The analysis observes no cases of serious gastrointestinal adverse events, and a low, but not clinically meaningful, incidence of minor gastrointestinal symptoms.

2014: Beginning with the launch in Germany (the birthplace of Aspirin™) New Aspirin™ is being introduced to consumers in countries throughout Europe and Latin America. The active ingredient of New Aspirin™, acetylsalicylic acid, is used in the form of microparticles that are on average 10 percent of the size of particles found in previous Aspirin™ tablets. Microparticles are combined with sodium carbonate, which acts as a disentigrant and local buffer, helping New Aspirin™ dissolve more quickly, enter the bloodstream faster, and relieve pain twice as fast as previous Aspirin™ tablets.

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Forward-Looking Statements
This release may contain forward-looking statements based on current assumptions and forecasts made by Bayer Group or subgroup management. Various known and unknown risks, uncertainties and other factors could lead to material differences between the actual future results, financial situation, development or performance of the company and the estimates given here. These factors include those discussed in Bayer’s public reports which are available on the Bayer website at www.bayer.com. The company assumes no liability whatsoever to update these forward-looking statements or to conform them to future events or developments.

25 Cooper SA., Voelker M., Inflammopharmacology 2012;20:225-242