



**Annual General Meeting
of Shareholders of Roche Holding Ltd
27 February 2006**

Address by Jan van Koeveringe
Head Pharma Global Technical Operations

(The address as delivered is definitive.)

Shareholders, Ladies and Gentlemen,

Around the world and at Roche, avian influenza and Tamiflu have been the focus of intense attention, and for Roche they remain a key issue. In my talk today I would like to add to what our Chairman has already said on the subject by looking at several facets in greater detail.

News stories about the geographic spread of avian influenza and the prospect of a lethal new 'super bug' sweeping the globe are a cause of widespread concern. The virulent H5N1 avian influenza virus has been spreading outwards from Asia since 2003 and has now reached Europe. Worldwide, the virus has claimed approximately 90 human lives to date.

Currently, we are dealing with a bird epidemic – in other words, a virus that causes disease in birds. The disease has, especially in Europe, so far only been diagnosed in birds in the wild. The few people in Asia to contract the virus so far have been people who have been in very close contact with infected birds. But nobody knows whether – and if so, when and where – the virus might undergo the mutations enabling it to be transmitted from person to person. What the experts do agree on is that the prospect of a pandemic is very real and that the risks are higher now than they have been in decades. So there is no question about the need for targeted preparedness activities that will make it possible to mount an effective response in the event of a pandemic – and there is no question that the time to prepare is now. This will involve adjustments that are both difficult and costly. Assuring the highest possible state of readiness will require decisions and action by governments and in the healthcare sector. Preparing for a pandemic encompasses a variety of measures, one of which is the stockpiling of antiviral medicines by national governments so that their countries' populations will have ready access to them when needed.

The threat of a human influenza pandemic poses a very special challenge for Roche, as our drug Tamiflu is *one* important element of pandemic preparedness. All the discussion devoted to avian influenza and Tamiflu serves as a reminder of how closely interconnected healthcare innovation and corporate social responsibility are. Roche has taken targeted action to fulfil that responsibility. Even before governments began stockpiling Tamiflu, we initiated a massive increase in production capacity for the drug at our own risk. By the end of 2006 Roche will be capable of producing over 300 million packs of Tamiflu a year – which is roughly comparable to

total production capacity in the influenza vaccine sector. You'll be hearing about our ongoing efforts to expand capacity further.

We have taken the initiative on four different fronts to help ensure the availability of Tamiflu. First, we have provided the World Health Organization (WHO) with a total of over 5 million packs of Tamiflu for rapid local deployment if needed. And we will continue to work closely with WHO.

Secondly, to help keep pandemic preparedness affordable, we have significantly reduced the price on deliveries for government pandemic use.

- Oseltamivir, the *active ingredient* of Tamiflu, is being supplied at highly reduced prices: industrialised countries pay € 7.70 per treatment course, and developing countries even less.
- Governments can also buy pandemic readiness supplies of Tamiflu in *capsule* form at a steep discount: industrialised and developing countries pay € 15.00 and € 12.00 respectively, or roughly 50 to 70 percent off the regular price. That is lower than the price we have seen quoted by generic manufacturers.

Thirdly, we have granted first sub-licenses for the manufacture of pandemic supplies of the Tamiflu active ingredient, oseltamivir, to companies in China and India.

Fourthly, we are conducting talks with a number of companies that could provide us with additional product manufacturing support if needed.

Tamiflu – a status report



- Discovered by Gilead 11 years ago
- Developed in record time
- Today available in 80 countries
- Originally developed for seasonal flu; now also being stockpiled for pandemic use
- Roche increases production capacity for the drug many times over
- Agreement between Roche and Gilead

For Roche, the Tamiflu story began in 1996, the year Roche acquired the global rights to develop and market the product from Gilead Sciences in California. After moving Tamiflu through development at top speed, we launched it in North America (US and Canada) and Switzerland in time for the 1999/2000 flu season. Launches in the major European markets followed three years later, in time for the 2002/2003 flu season.

To date, over 34 million people in roughly 80 countries around the globe have been treated with Tamiflu. The product won't go off patent until 2016.

If I may, I'd like to spend a little time providing some general background information on influenza.

'Influenza', the medical name for what is usually just called 'the flu' in everyday speech, comes from the Latin word *influen*, meaning 'to flow in', or sometimes 'to creep in'. 'Real flu' is a severe acute viral respiratory infection accompanied by fever. Unlike colds and other flu-like illnesses, influenza is a serious, potentially fatal disease.

The term 'grippe', which is disappearing from English but is still widely used in other languages, comes from French, where it originally meant a whim or mood. The word probably acquired its

medical sense because of influenza's sudden onset and the unpredictable way in which it strikes some people while sparing others.

Influenza is characterised by the sudden onset of fever, coughing, fatigue/weakness, headache and aching muscles. The acute phase of the illness lasts five to seven days, but fatigue and weakness may bother the patient even longer.

Influenza is an epidemic disease, i.e. it generally affects large numbers of people in a given area at the same time; and it usually strikes during the cold months of the year. An epidemic affecting populations around the globe is called a pandemic.

In the past influenza pandemics have occurred at intervals of from 10 to 40 years. During an influenza pandemic up to 50% of the population may become infected with the causative virus, and the death toll can be in the millions.

Signs and symptoms of real flu

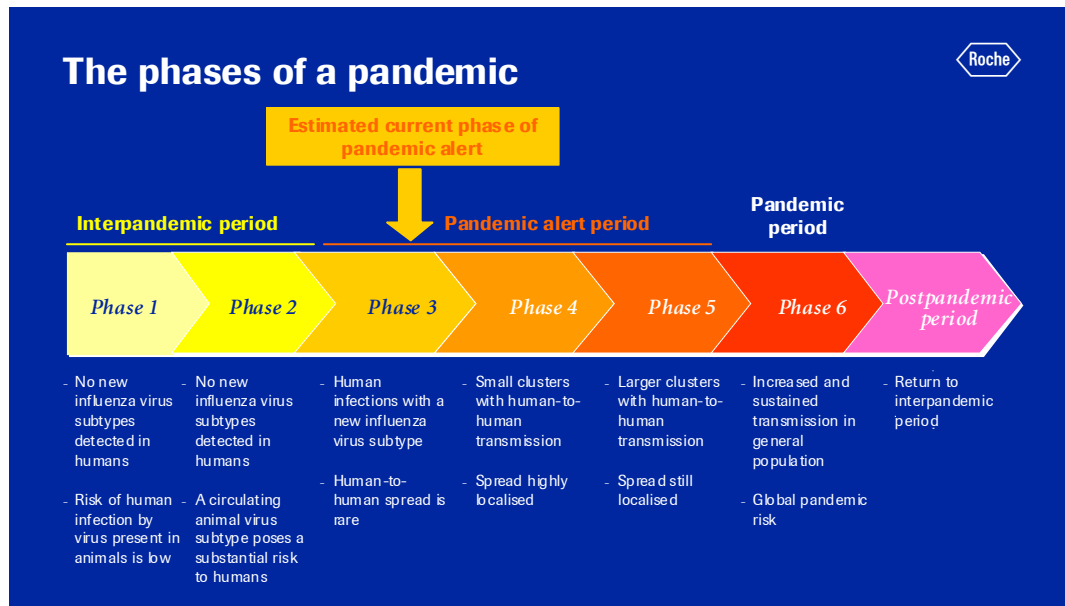


- Sudden onset of illness
- Bad cough, headache, muscle ache, fever/chills and fatigue/weakness
- Acute respiratory symptoms can last five to seven days
- Fatigue and weakness can persist for two to three weeks

The 20th century witnessed three major influenza pandemics, the most devastating of which occurred in 1918–1919 and is remembered as the Spanish flu. Worldwide, the Spanish flu probably claimed between 20 and 50 million human lives. The Asian flu pandemic (A/H2N2) in the 1950s killed approximately 1 million people. And more than 800 thousand were killed by the Hong Kong flu (A/H3N2) in the 1960s.



The World Health Organization (WHO) estimates that the next influenza pandemic will result in about 7 million deaths.

According to WHO, an influenza pandemic occurs when a new strain of influenza virus A emerges to which people have little or no immunity. As a result, multiple epidemics occur simultaneously in populations around the globe, with high morbidity and mortality.



A pandemic can be broken down into six phases. Experts believe we have reached the end of phase 3, which means that an influenza pandemic is very likely in the near future.

Tamiflu – the product



- Tamiflu
 - is an oral antiviral medicine (neuraminidase inhibitor)
 - is not a vaccine
 - is active against all clinically relevant influenza virus strains
 - inhibits the viral enzyme neuraminidase; as a result, influenza viruses are unable to replicate and spread inside the body
 - has demonstrated activity against the H5N1 avian influenza virus in animal models
- Active ingredient: oseltamivir (produced by chemical synthesis)
- Dosage forms: capsules, syrup
- People with suspected influenza should consult a doctor immediately. Tamiflu has to be started within 48 hours of the onset of symptoms.
- Treatment course: 10 capsules; 1 capsule twice daily

Now I'd like to say a bit more about Tamiflu itself. Tamiflu (oseltamivir) is not a vaccine, but an oral antiviral medicine for influenza, and belongs to a class of drugs known as neuraminidase inhibitors. These medicines inhibit a viral enzyme called neuraminidase, thus preventing influenza viruses from spreading inside the body. Tamiflu can be used for the treatment and prevention of influenza in adults and in children aged one year or older.

Tamiflu is a prescription medicine given in capsule form (or as a syrup in children). The usual dose for treatment of influenza in adults is one 75 mg capsule twice daily for five days. A pack of Tamiflu contains a full treatment course of 10 capsules. For full efficacy, treatment needs to be started within two days of the onset of symptoms.


When taken twice daily for five days, as recommended, Tamiflu can reduce the severity of patients' symptoms and the likelihood of flu-related complications like bronchitis and pneumonia, and it can hasten recovery.

Moreover, deaths among influenza patients treated with Tamiflu – whether adults or children – is lower than among patients not treated with the medicine. According to independent studies, treatment with Tamiflu reduces mortality in children by 60 to 90 percent.

Tamiflu – for treatment and prevention of influenza

- The only neuraminidase inhibitor for oral use
- Reduces the severity and duration of symptoms
- Can reduce the risk of pneumonia and death

One death reported in 39,202 patients who took oseltamivir



versus

Fifty-eight deaths among 136,800 patients not treated with antiviral medication

Leading international research groups that have investigated the efficacy of available antivirals against avian H5N1 influenza in animal models have demonstrated that Tamiflu is active against this viral strain.

As you know, there is no vaccine as yet for this influenza virus strain, so Tamiflu is an important therapeutic option. Roche recommends that approved dose and duration of treatment/chemoprophylaxis represents the minimum required for the management of pandemic influenza.

Additional studies are under way to assess the antiviral activity of Tamiflu against the H5N1 avian influenza virus on a broad, ongoing basis. We are also in discussions with WHO about trials that could provide additional clinical data.

Roche is working with WHO

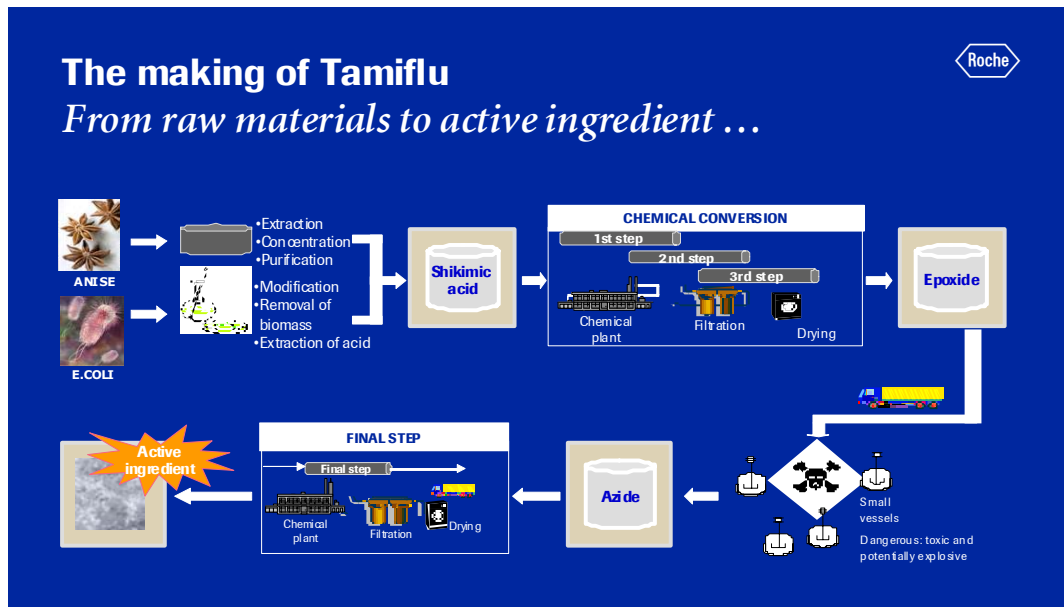


- Over 5 million packs of Tamiflu donated so far
- In the event of an outbreak of pandemic influenza, Roche will ship supplies of the drug at its own cost to the airport nearest the outbreak site
- WHO is working with local government authorities on distribution

We are in constant contact with WHO and have been able to respond quickly in supplying Tamiflu to potential hot spots where the drug has been urgently needed.

Following the donations we made in 2004 and 2005, the 2 million additional packs of Tamiflu that we donated to WHO in January of this year bring WHO's total stockpile of Tamiflu for use in the event of an imminent pandemic to roughly 5 million packs. These supplies are an emergency stockpile, and should not be regarded as a substitute for national pandemic preparedness measures.

In closing, allow me to say a word or two about how Tamiflu is manufactured and about our production capacity for the drug. The amount of detailed information we've published on these topics is unprecedented and reflects both the intense global interest in the subject and the global importance of the product.

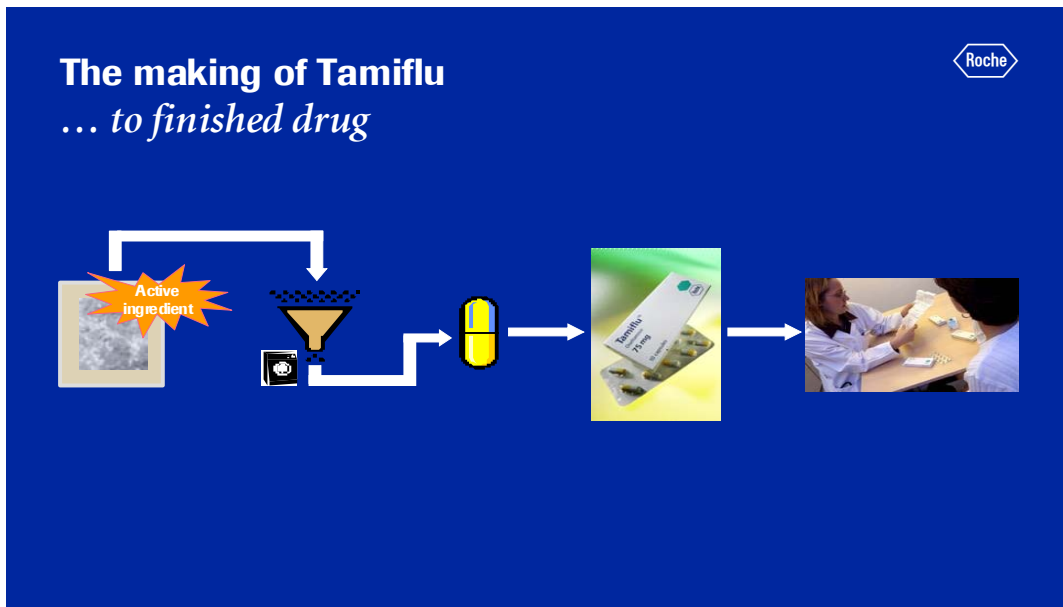


Manufacturing Tamiflu is a complex process involving 10 main steps, some of which are quite challenging.

The starting material used to produce Tamiflu is shikimic acid, which is either extracted from star anise pods or obtained by fermentation (i.e. using biotechnology). This material is sourced from outside suppliers.

At present, most of the shikimic acid used to make Tamiflu comes from star anise. However, we intend to raise the proportion obtained by fermentation. This will make us less dependent on the (limited) supply of star anise.

Shikimic acid is used to produce an epoxide intermediate, which is then to an azide. The dependence on 'azide chemistry' in this part of the production process necessitates the use of special equipment and specially trained staff. Conversion of the epoxide to the azide has to be carried out under highly controlled conditions because it involves a potentially explosive reaction. Our facilities are not equipped for this part of the production process, which we therefore entrust to partner companies with expertise in this area. The azide is then used to produce oseltamivir, the active ingredient of Tamiflu.



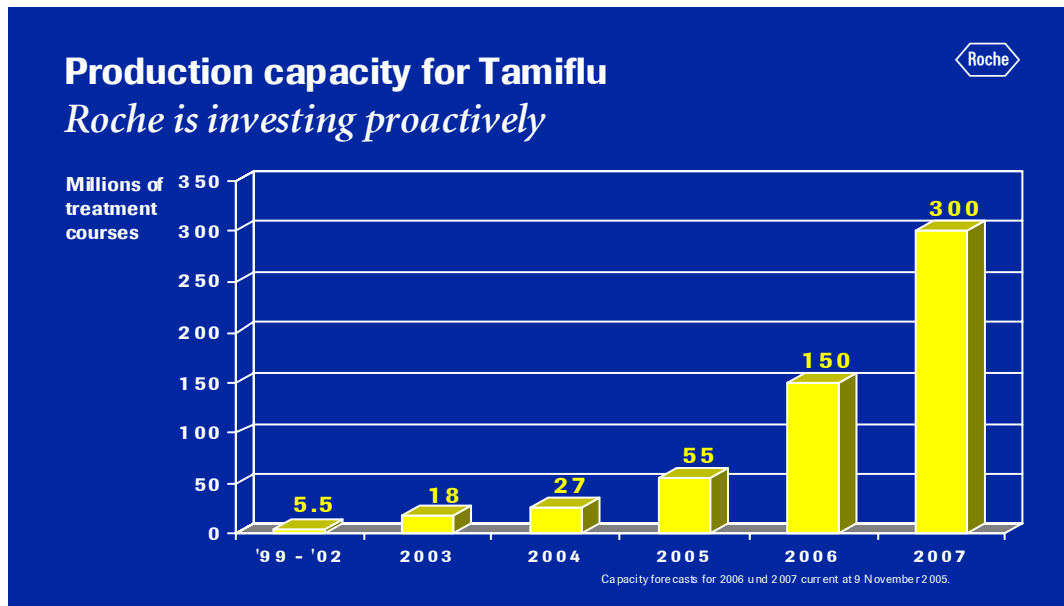
The resulting white oseltamivir powder is filled into capsules after being granulated to improve its flow properties. The alcohol granulation process registered for this product is a bit atypical for the pharmaceutical industry, and only a limited number of facilities are equipped to carry it out on a commercial scale.

We are currently conducting talks with a number of companies that have the appropriate facilities and know-how for specific production steps and that could help us expand our supply chain further, if need be.

Strong public interest in the avian influenza situation has resulted in increased demand for Tamiflu from various sectors, including private individuals and institutions. Our top priorities are to ensure that Tamiflu is available to seasonal flu patients and to fill government orders for pandemic readiness supplies.

So far we have agreed on volumes and delivery schedules with more than 65 countries that are stockpiling Tamiflu for pandemic use. Because of the strong demand and manufacturing lead times for Tamiflu, we have expressly stated that it would be unrealistic to expect that large Tamiflu orders can be filled at short notice.

Worldwide, more than a dozen production facilities are involved in the Tamiflu supply chain today, and over half of them are operated by companies other than Roche. The raw materials and excipients required to make Tamiflu are being sourced from over 50 outside suppliers. Further capacity increases will be achieved by expanding our production network step-by-step.



With the help of partner companies, we will significantly increase our own production capacity this year, putting us in a position to produce over 300 million packs of Tamiflu annually by the end of 2006. The expansion will be achieved by a further stepwise scale-up of Roche's production network, both internally and together with third parties, and means a ten fold increase over the capacity in 2004.

A responsible response



- Healthcare innovation and corporate social responsibility are intertwined. At Roche we take social responsibility seriously.
- We have donated a total of over 5 million packs of Tamiflu to the World Health Organization (WHO) for rapid local deployment if needed.
- Governments worldwide can purchase pandemic supplies of Tamiflu at a significant discount.
- Sub-licenses to manufacture supplies for local pandemic use have been granted to companies in China and India.
- By the end of 2006 Roche will be able to produce more than 300 million packs of Tamiflu annually.
- Production planning has our full attention.

Ladies and Gentlemen, avian influenza and the threat of a human influenza pandemic are challenges confronting the entire global community. In developing Tamiflu, our company has supplied a product with an important role to play in pandemic preparedness and response efforts. I can assure you that we do everything we can to live up to the responsibilities this entails.