

## Vaccines for pandemic influenza

Informal meeting of WHO, influenza vaccine manufacturers, national licensing agencies, and government representatives on influenza pandemic vaccines

### *SUMMARY REPORT*

*11–12 November 2004  
Geneva, Switzerland*

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## *Summary report*

### **INTRODUCTION**

Since January 2004, outbreaks of highly pathogenic avian influenza, caused by the H5N1 strain, have raised concern that the world may be moving towards another influenza pandemic. As part of its response to this concern, WHO hosted a high-level meeting, held in Geneva from 11 to 12 November, to explore ways to expedite the development of pandemic vaccines. The meeting, which was convened on an urgent basis, was attended by representatives of all the major influenza vaccine manufacturers, health ministries in several countries, licensing agencies in Europe and North America, and laboratories in the WHO Global Influenza Surveillance Network. Participants were asked to review the status of vaccines for an influenza pandemic, identify obstacles and explore solutions.

An overview of the present situation was provided on the first day. Participants reported on the status of pandemic vaccine development in individual companies, described national preparedness activities, including efforts to secure adequate vaccine supplies, and outlined regulatory issues unique to pandemic vaccines. Participants readily agreed that vaccines would be the most important tool for reducing the high morbidity and mortality invariably associated with pandemics. All presentations took a pragmatic approach, identifying obstacles and looking for concrete solutions that could help ensure the availability of vaccines as quickly and in as large a quantity as possible from the beginning of a pandemic.

The first session of the second day was devoted to discussion of problems and potential solutions proposed by three working groups. These proposals were further discussed during the final plenary session, where participants reached consensus on main conclusions from the meeting.

This report has two parts. The first, on conclusions, presents the main conclusions of the meeting, agreed on by consensus, followed by a summary of conclusions reached by the working groups. The second part, compiled by the WHO secretariat, summarizes points made during the various presentations and the issues raised during their subsequent discussion. This summary is included as background to the main conclusions. The level of agreement reached reflects the spirit of the meeting: a determination, despite different responsibilities of the participants and their different perspectives, to forge solutions on the brink of a possible global health emergency.

# 1 CONCLUSIONS

## Conclusions from the meeting

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### **Vision for influenza pandemic vaccines**

- A world adequately prepared for an influenza pandemic would have governments in all countries engaged, according to their ability, in preparedness activities, including vaccine development.
- Adequate preparedness includes having safe and effective pandemic vaccines available during the initial phase of a pandemic, with as much vaccine available as early as possible.

### **Prerequisites for success**

- Efficient surveillance for novel influenza viruses and for unusual clusters of respiratory infections in humans should be in place in all regions.
- Laboratories in the WHO influenza network should maintain their capacity to select and prepare vaccine prototype strains.
- Increased vaccination coverage during seasonal epidemics should be recognized as the best long-term strategy for ensuring an adequate manufacturing base for pandemic vaccines; national policies should seek to improve vaccination coverage of groups at high risk of complications during seasonal epidemics.
- Studies should be conducted to evaluate antigen-sparing strategies.
- All vaccine companies should license a “mock-up” pandemic vaccine.<sup>1</sup>
- Industry needs to address issues of intellectual property rights for patented technologies, including reverse genetics. While these issues should not impede seed development and clinical trials, they will come into play at the stage of commercial production.
- National policies should be put in place to guide the priority use of a pandemic vaccine and this guidance should be adapted as the epidemiology of the pandemic becomes apparent.
- WHO should improve global awareness of the threat from pandemic influenza and its consequences as a strategy for encouraging more governments to engage in preparedness activities, including vaccine development.

### **Immediate actions**

- Clinical trials to establish vaccine formulation should be coordinated internationally to facilitate the exchange of non-proprietary pre-clinical and clinical data and of information on strain choice.
- Antigen-sparing strategies should be systematically evaluated as a high priority; these strategies, which use adjuvants to enhance the effectiveness of antigen and thus stretch limited supplies, probably represent the best hope that non-vaccine-producing countries will have access to vaccine.

- Coordination at the regulatory level is needed to improve the regulatory environment and facilitate international marketing of vaccines.
- Coordinated efforts are needed to increase funding for the development of a pandemic vaccine as a global public health good.
- All manufacturers should develop internal contingency plans to expedite the switch from production of seasonal vaccines to pandemic vaccines. Such plans should include the testing of “mock-up” pandemic-like vaccines according to established regulatory procedures.
- More companies should be encouraged to move pandemic-like vaccines through the development and registration process.
- In the absence of market incentives to produce pandemic-like vaccines, health authorities should seek ways to encourage vaccine development and licensing as, for example, through waiving regulatory licensing fees, financing clinical trials, and offering tax incentives.
- Governments should assume responsibility for liability following adverse events or failure of the vaccine to confer adequate protection.
- Consideration should be given to the establishment of national and international stockpiles of bulk antigen, for subsequent formulation in a pandemic vaccine, as such stockpiles would allow immediate start of vaccination following emergence of a pandemic virus. Production of such reserve antigen supplies should not, however, compromise production capacity for seasonal vaccines.

### **Summary conclusions from the working groups**

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Conclusions reached by the three working groups were presented and discussed on the second day. Each working group was given the same charge: to assess the present situation, define roles and responsibilities, identify the main obstacles, and propose solutions. The individual working group reports were discussed in plenary. Obstacles identified and solutions proposed formed the basis of main conclusions agreed upon during the meeting.

**Current situation.** While the past year had seen substantial progress, the present capacity to produce a pandemic vaccine was considered woefully inadequate. Should a pandemic start tomorrow, manufacturing capacity would not be able to meet global demands. Moreover, location of current capacity (concentrated in Europe, North America, Australia and Japan) would allow vaccination of only a small minority of the world’s population.

The many unknowns associated with the occurrence of pandemics also apply to vaccine manufacturing. No one can fully predict how prototype vaccine strains now under development will behave under the conditions of large-scale production. It is likewise uncertain if vaccine production could be increased by using antigen-sparing strategies, thus making the most out of limited virus antigen. Clinical trials with an H5N1 prototype strain derived from currently circulating virus have not begun, and this leaves many unanswered questions. Would a two-dose schedule be needed? Could antigen content be reduced? Would an adjuvanted vaccine bring the hoped-for advantages? In the end,

production capacity will depend on answers to all these questions, which need to be addressed by research.

**Roles and responsibilities.** Concerning roles and responsibilities, governments were urged to provide a better environment for the development of influenza vaccines in general, most notably by increasing the uptake of seasonal vaccines, when this conforms with national health priorities. It was up to countries with resources and manufacturing capacity to prepare the stage for responding to what would unquestionably be a global threat. A balancing of national interests against global needs would be needed. Government assumption of responsibility for liability in the event of possible adverse reactions or inadequate protection from vaccine use during mass vaccination was needed. Solutions to the difficult issue of priority groups for limited supplies should be worked out now rather than during the chaos of a pandemic.

Governments were further asked to support industry initiatives with financial incentives, and examples of these were given. To pave the way for international marketing of vaccines, regulatory agencies should coordinate their licensing and registration requirements. Coordination between European and North American agencies had been discussed, and this discussion should be extended to include other agencies, such as those in Russia and China.

Although the principal influenza vaccine manufacturers were linked together by their influenza vaccine supply task force, more could be done to foster coordination and sharing of non-proprietary data. For example, some companies indicated their willingness to share clinical and pre-clinical data. As another preparedness measure, more companies should develop internal contingency plans.

Academic institutes could contribute by conducting essential research in immunology and virology, producing mathematical models, and assessing the likely economic impact of a pandemic. Public awareness of the issues would either hold governments accountable for the adequacy of preparedness plans, or – at the other extreme – permit them to remain complacent.

Pandemic influenza was considered by many to be the ultimate global public health emergency. WHO leadership, supported by the network of influenza laboratories, would be put to an extreme test, as would national response capacities. In the meantime, WHO could do much, in its international coordinating role, to improve the level of preparedness. Apart from coordination of clinical trials and establishment of priorities for international research, WHO could enhance global awareness of what might be an imminent humanitarian crisis. This heightened awareness, in turn, might persuade commitment on the part of more governments and stimulate a demand from their citizens for greater preparedness activities.

**Obstacles and solutions.** With so much left to be done, coordination was essential to prevent duplication of efforts and foster the sharing of experiences. Two priority areas for international coordination were identified: clinical trials to establish vaccine formulation, and coordination of regulatory requirements.

Coordination of clinical trials should allow sharing of pre-clinical and clinical data and of information on strain choice. Good scientific data, derived from

studies with adequate numbers and proper controls, were particularly important to answer questions about antigen content, immunogenicity, routes of administration, and the performance of adjuvants. Antigen-sparing strategies should be systematically evaluated (taking into account requirements for individual production processes) in advance and given high priority, as these probably represent the best hope that non-vaccine-producing countries will have access to vaccine. Documentation on safety and effectiveness was needed.

Coordination at the regulatory level could help align regulatory processes from different countries, to the extent possible, by defining likely requirements for demonstrating adequate immunogenicity, exploring possibilities for simplified release tests, and coordinating the testing and assessment of assays.

More companies were encouraged to move pandemic-like vaccines through the registration process, and governments were asked to provide the necessary financial incentives. Apart from increasing the uptake of seasonal vaccines, governments could, for example, waive regulatory licensing fees, finance clinical trials, and offer tax incentives. Governments could also move the process forward by assuming responsibility for liability and using national institutes to conduct essential clinical research. Orders for reserve antigen supplies were another incentive. Apart from providing countries with strategic pandemic vaccine stocks for emergency use, this option would allow industry to test production systems at commercial scale, while also addressing other technical and regulatory issues.

## **2 SUMMARY OF PRESENTATIONS AND DISCUSSIONS**

### **The issues: urgency despite uncertainty**

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Several general observations were made repeatedly from different perspectives. Participants shared the view that the next pandemic is overdue and could be imminent, and their discussions reflected this sense of urgency. All agreed that the timing of a pandemic could not be predicted. Nor was it certain that a variant of H5N1 would be the causative agent. For example, as some participants noted, the H9N2 strain has also shown some pandemic potential. These and many other uncertainties made firm commitments on the part of governments and industry, and creation of the appropriate level of public concern problematic.

Some suggested that WHO could do more to raise awareness of the pandemic threat and its considerable consequences for economies and societies as well as for public health. Good scenarios of projected morbidity and mortality might persuade governments to give higher priority to pandemic preparedness; certainly, more nations with adequate resources needed to be engaged in these activities. When viewed against the likely costs of a pandemic, the current levels of investment needed to advance preparedness would look very small. In addition, reasonable forecasts of vaccine need, target populations, and patterns of international spread could help industry anticipate demand.

**Unknown factors.** Again, the reliability of such estimates was clouded by many unknowns. Would the next pandemic be comparatively mild, as in 1968, or catastrophic, as in 1918 – the most deadly disease event in recent human history? If populations were immunologically naïve to the new virus, would two doses of vaccine be needed to confer adequate protection? Would severe outcome from disease affect mainly children and adolescents (as has been the case with H5N1) or would it be confined to the traditional risk groups – the elderly, the very young, and those with underlying chronic disease? Or would healthy young adults experience the highest mortality, as occurred in 1918? These unknowns would affect vaccine demand and delivery strategies; firm answers must await emergence of the pandemic virus and demonstration of its epidemiological potential.

In a situation characterized by urgency and uncertainty, participants noted the need to define roles and responsibilities in a process of risk-sharing, for vaccine development and production, and to work on different tasks in parallel, and not sequentially. Discussions were taking place in uncharted territory: never before had a pandemic been preceded by a warning signal, such as that sounded by the H5N1 avian influenza outbreaks in Asia; never before had industry, regulatory agencies, and governments had an opportunity to find joint solutions on the possible brink of a pandemic.

As several participants noted, it was far more sensible to explore options now than during the chaos of a pandemic; such advance efforts are the only way to secure at least some vaccine supplies for use at the start of a pandemic. This was also the best time for collaboration – internationally among countries, within the vaccine industry, and between governments and industry. Judging from past experience, the problems that would arise during an influenza pandemic would be too great for any single country or vaccine company to handle. In these exceptional circumstances, any coordination or collaboration that could move the process of vaccine development forward should be given high priority, as many lives could be saved by timely supplies of vaccines. In some, but not all, areas, it was felt that WHO could most appropriately play a coordinating role.

**The greatest need: production capacity.** Whatever the scenario and whatever the reality, participants agreed that the biggest problem was inadequate influenza vaccine production capacity. Many proposals – for both immediate and later application, involving tried-and-true technologies and forward-looking innovations – were presented and discussed as participants sought ways to minimize manufacturing delays and maximize production capacity.

Health officials and industry executives were in full agreement that increased use of vaccines for seasonal epidemics represents the best long-term strategy for increasing manufacturing capacity for pandemic vaccines. It also mitigates the considerable health impact of seasonal influenza epidemics (an estimated 250,000 to 500,000 deaths globally) and makes the supply of vaccine for this purpose more secure. Increased use of seasonal vaccines gives countries experience in the logistics of vaccine administration; to date, influenza vaccination in most countries with national policies has concentrated on reaching high risk groups.



While no one questioned the practical and public health value of this long-term strategy, some raised the obvious question: how would capacity problems be solved if a pandemic virus emerged right now?

On the technical side, it was generally agreed that antigen-sparing technologies held great promise as a strategy for maximizing the number of doses in view of limited manufacturing capacity. Some felt that this approach offered the best hope that non-vaccine-producing countries, including developing countries, could secure some vaccine supplies early enough to make a difference in morbidity and mortality rates. However, antigen-sparing vaccine formulations need to be evaluated through coordinated research. Answers to these and several other technical questions will ultimately determine the timing and quantity of supplies. The chance of having effective vaccines available quickly would be greatest when companies rely on familiar technologies, backed by experience, when developing pandemic vaccines.

### **The public health perspective**

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Presentations representing the public health perspective, as expressed by ministries of health, drew attention to specific activities undertaken as part of pandemic preparedness planning, emphasizing the role of vaccines and the status of efforts in participating countries to secure adequate supplies. All countries represented at the meeting had domestic manufacturing capacity. Clearly, countries with domestic capacity were one step ahead, and those benefiting from government funding of investigational vaccines and clinical trials were yet another step ahead. Participants from the USA, Canada, and Japan described government policies and specific investments that were supportive of pandemic vaccine development. Manufacturers in the USA and Japan are expected to move investigational vaccine into clinical trials in 2005, though US manufacturers will do so earlier than those in Japan.

In the USA, government contracts with two companies (Aventis Pasteur and Chiron) have supported the production of pandemic-like vaccine and clinical trials, which will begin in early 2005. The government has also placed an order for bulk antigen sufficient for the formulation of 2 million doses of an H5N1 vaccine (15µg/dose). This small strategic stock requires manufacturing at commercial scale, and thus benefits the manufacturer as an important test of its production system and for necessary stability testing. Vaccine formulation would have to await the results of clinical trials. The US government was also providing support for reserve hen flocks and for advanced development of cell-culture based vaccines.

In 2001, as part of its comprehensive pandemic plan, Canada established a 10-year contract with ID Biomedical Corp. for annual vaccine supply and pandemic preparedness. Government funding involves a sharing of infrastructure costs for pandemic vaccine production and payment of an annual "pandemic readiness fee". Pandemic readiness further stipulates a capacity to produce eight million doses of monovalent vaccine per month for four months. The Canadian plan recognizes the need to test the production system and facilities with a pandemic-like vaccine to expedite product licensing.

Japan, which has four national influenza vaccine manufacturers, has increased government funding for influenza vaccine-related research and opened a fast-track pathway for pandemic vaccine licensing. Clinical trials were expected to start in the second half of 2005, with product submission to regulatory authorities scheduled for 2006. As an emergency first-line of defence, the Japanese strategy included granting a limited license, at the start of a pandemic, for a vaccine that would be administered to priority groups only.

These efforts went hand-in-hand with campaigns to improve uptake of seasonal vaccine; several countries (Canada, Switzerland, the UK, and the USA) reported impressive progress in this regard. In France, where the 400,000 deaths from the 1918 pandemic were still vividly recalled, the government had plans to purchase sufficient pandemic vaccine to cover 50% of the country's population; antiviral drugs sufficient for 3 million treatments were being stockpiled. Switzerland, which was home to a principal antiviral manufacturer, would ensure sufficient supplies of antiviral drugs to protect its population. That country had a national vaccine production site that could be activated should the need arise.

Concerning the need for government investment, some participants recalled the reality: pandemic vaccine development would not happen spontaneously in the absence of market forces. Governments may need to regard pandemic vaccines as a public health good. Should governments not step in for this reason, they could face criticism by their citizens once a pandemic began to take its toll. One speaker recalled an appropriate truism: the only thing more difficult than planning for an emergency is having to explain why you did not plan.

Participants from the USA, Canada, and the UK all mentioned the importance of high government appreciation for the threat posed by emerging infectious diseases in general and pandemic influenza in particular. In this regard, concern about a possible bioterrorist attack had initially sensitized politicians to the impact that a severe contagious disease could have in a highly mobile and closely interconnected world. SARS demonstrated these theoretical concerns in stark reality. These events had primed politicians to acknowledge the importance of pandemic preparedness and made them familiar with the issues, including the similarities between pandemic planning and planning for other infectious disease emergencies. Canada, in particular, had promoted pandemic preparedness as a national health security issue.

In countries such as Australia and Japan, their geographical proximity to the 1997 H5N1 scare in Hong Kong and this year's recurrence of cases in Asia had impressed politicians with the immediacy of the threat. This no doubt helped raise the level of government concern and stimulated efforts to have a pandemic vaccine ready.

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## **The industry perspective**

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Industry was well acquainted with the technical, regulatory, and public health issues that surround the development and production of pandemic vaccines. In 2002, a group of manufacturers formed a task force to address supplies of influenza vaccine, including pandemic vaccine. There are presently 14 companies in the task force; collectively, they produce more than 90% of the total supply of influenza vaccines globally. In the view of industry, development

of a pandemic vaccine was a challenge to industrial technology and innovation. Commitment to meeting this challenge was expressed. That challenge, however, was great. In particular, the development and manufacturing of a vaccine effective against H5N1 (or other potential pandemic viruses) is subject to unique risks and constraints, and these have a direct impact on questions of availability and capacity as well as timeframes.

As industry has to update the formulation for seasonal vaccines almost every year, the steps needed to move a candidate pandemic vaccine along the development pipeline to full-scale commercial production were well-known but would need to be tested. Industry could offer its considerable experience, technical know-how, facilities, and staff, but corporate funding would not be available for development of a product that might never reach the market. Nor could production of a vaccine for a future threat take priority over production of vaccines immediately needed.

In addition, the H5N1 virus – which presently has the greatest pandemic potential of any animal influenza virus – brought its own set of distinct challenges for vaccine development and production. This highly lethal avian virus cannot be grown in fertilized chicken eggs (the traditional method of vaccine production) and required modification. The technology of reverse genetics is needed to remove lethal genes. Reverse genetics involves patented technologies, introducing issues of intellectual property rights, and these need to be anticipated and addressed in advance. In Europe, a vaccine produced using reverse genetics is considered a genetically modified organism, introducing additional biosafety requirements for manufacturing facilities. High lethality for humans further means that work to develop a seed strain must take place under heightened biosecurity conditions. These added requirements impede the manufacturing process and further constrain capacity, as not all manufacturing facilities are equipped to operate at the higher biosafety level; upgrading of facilities is possible but costly and time-consuming, requiring at least one year to achieve.

**Partnerships needed in specific areas.** Industry identified five main areas in which public-private partnerships were needed to move the process forward: (1) development of the seed vaccine and registration of a mock-up product, (2) expansion of production capacities, (3) assurance of adequate supplies and equitable distribution, (4) acceleration of time to market, and (5) assurance of liability protection.

(1) Seed vaccine and registration. Companies with government contracts to produce investigational vaccines and conduct clinical trials were presently in the best position to move products through registration and answer key questions about formulation. Better international coordination of regulatory requirements would facilitate licensing, especially for foreign markets.

(2) Expanded capacity. Vaccine formulation – antigen content, adjuvants, immunogenicity, and dose schedule – would ultimately influence the number of doses available. Furthermore, increased uptake of seasonal vaccines would profoundly expand global manufacturing capacity. This could be achieved through government policies aimed at meeting WHO recommendations and targets for seasonal vaccine coverage in high risk groups in countries where

influenza vaccination is part of national priorities for combating infectious diseases.

(3) Supplies and distribution. Industry was keenly aware of the problem of inadequate supply and inequitable distribution. Again, increased uptake of seasonal vaccines was the best long-term strategy for increasing overall capacity. It would be up to governments in countries with domestic manufacturing capacity to determine whether vaccine would be exported during an emergency; these questions could not be addressed by industry. Better clarity on government policies would be useful for industry in anticipating markets.

(4) Time to market. Industry needs partners to anticipate all logistical problems and work out solutions. Filling capacity, for example, could be a bottleneck, as could inadequate supplies of syringes.

(5) Liability protection. Liability issues would certainly arise for a product developed quickly, under great pressure, and in massive quantities for administration on a mass scale. Apart from adverse events that will be reported after vaccination (whether caused by the vaccine or coincidental), liability issues might arise should a vaccine fail to confer adequate protection. For these reasons, industry needed advance assurance that governments would provide liability protection.

Intellectual property rights were another potential problem for patented technologies, such as reverse genetics. While industry believes these issues will not delay vaccine development, they would come into play at the stage of commercial production. Industry was deeply familiar with intellectual property rights and would know how to handle the issues in advance. Intellectual property rights would, however, have cost implications for commercial vaccines.

**Options being pursued.** In anticipation of a pandemic, individual companies had been moving forward in pursuit of a diversity of technical solutions and manufacturing options. Steps to improve preparedness ranged from the construction of new plants meeting higher biosafety standards, through investigation of adjuvanted vaccines as an antigen-sparing technology, to the development of libraries of candidate vaccine prototypes.

Some companies are preparing to use newer production plants and technologies, including cell-culture vaccines using new cell lines, within the next few years. These newer technologies represent the way industry would move in the future for the production of both seasonal and pandemic vaccines. In the short term, however, reliance on existing technologies, backed by experience, was considered the best way to develop as many candidate vaccines as quickly as possible in compliance with existing regulatory requirements. By using what is best known, companies felt they could reduce the risk of surprises when moving into full-scale commercial production under the pressures of an emergency. The use of adjuvants to increase vaccine supply, despite finite capacity, was based on several attractive assumptions. These advantages were still only potential at this stage and could not be exploited without coordinated clinical trials.

Presentations from the various companies supported an obvious conclusion: there would be no single vaccine prototype strain, and many different seeds prepared by different companies, many different vaccines produced by different

technologies, and many different formulations (antigen content, adjuvants). To reach their maximum capacity, companies would need to operate with their preferred technologies. Standardization of pandemic vaccines will rely on the same principle used for all epidemic vaccines: measurement of antigen content. However, such standardization would not rule out the possibility that one vaccine might prove more advantageous in clinical use than others.

In Japan, where three of the four manufacturers were non-profit enterprises, the development of a pandemic vaccine was being driven by the government. For example, the National Institute of Infectious Diseases had undertaken investigation of an H5N1 virus seed. Work to date suggested that an aluminium-adjuvant whole virion vaccine might provide the highest immunogenicity. However, there was some indication that production efficiency may depend upon the specific vaccine prototype strain used. Several small batches of an H5N1 vaccine were being produced for investigational purposes, with clinical trials scheduled for the latter half of 2005. Collaboration among Japan's manufacturers would assist in assessing various types of test vaccine and screening for the most effective.

Manufacturers in Canada (ID Biomedical Corp.) and Australia (CSL Limited) described their favourable ratio of production capacity to domestic population needs. Both companies anticipated rapid meeting of domestic needs, with significant surplus capacity available for foreign markets. The Australian company had built new biosafety-level 3 facilities, and could start production in April 2005, provided funding for clinical trials was secured.

Some companies are investing in the development of cell-culture vaccines; advantages include an acceleration of vaccine development and faster scaling up of capacity. GlaxoSmithKline is the first company to finalize clinical trials with a pandemic vaccine strain (H2) and will submit the dossier for registration shortly.

MedImmune, which holds the patent on the reverse genetics technology, would produce a live attenuated vaccine. Baxter reported good capacity, Vero cell technology, and new facilities, also for working with highly pathogenic viruses, but no corporate funding for pandemic vaccine development, as neither the size of the market nor timing of demand was known. Baxter judged its capacity as sufficient to manufacture 40 to 50 million doses of a trivalent seasonal vaccine per year.

Aventis Pasteur is presently engaged in the largest number of initiatives to move pandemic vaccine development forward in Europe and North America. Some of these initiatives have been supported by contracts from US government agencies. A cell-based vaccine with and without adjuvant was under investigation and a proposal had been submitted to accelerate licensing of vaccines produced with these technology. Chiron, which also had contracts from US government agencies, had produced investigational doses of vaccine from an H5N1 seed produced using reverse genetics.

## The regulatory perspective

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For regulatory agencies, seasonal vaccines pose a particular challenge because of the need for rapid strain adaptation. Established regulatory procedures make it possible for a safe “new” vaccine to be produced and delivered twice each year. Seasonal influenza vaccines are a familiar product, and their production and licensing follow well-rehearsed procedures. During the previous year, the Food and Drug Administration (FDA) of the USA and the European Medicinal Evaluation Agency (EMA) have outlined regulatory pathways for the licensing of pandemic vaccines. This step has given individual companies a predictable environment for planning vaccine development and production.

Presentations describing European and North American regulatory perspectives revealed some important differences. For example, the FDA would regard pandemic vaccine in the same way that yearly strain variations are treated, provided the pandemic vaccine was manufactured by a company with a licensed product on the US market. Issues of dose and immunogenicity would, however, need to be specifically addressed. Should the pandemic vaccine require new manufacturing technologies or different formulations (such as use of adjuvants), the regulatory situation would no longer be as straightforward. For this reason, it would be important to develop the required data on safety, immunogenicity, and effectiveness in advance of a pandemic.

In Europe, the EMA has published documents providing scientific and procedural guidance to influenza vaccine manufacturers on the structure of the dossier and the content of marketing authorization for pandemic vaccines. In addition, a centralized procedure exists, supported by guidelines for submissions for marketing authorization for pandemic vaccines. As pandemic vaccines will differ in their formulation (antigen content, adjuvants, number of doses), use of data extrapolated from clinical testing of seasonal vaccines is not considered acceptable by EMA. Clinical trials with a “mock-up vaccine” are therefore required to demonstrate safety and immunogenicity and to establish dose and dosing schedule.

It was agreed that the different licensing concepts for pandemic vaccines should be reviewed in advance. Greater international consistency would create the enabling environment needed for international marketing of vaccines.

<sup>1</sup>A “mock-up” pandemic vaccine, also referred to as a “pandemic-like” vaccine, is a vaccine that anticipates and mimics the characteristics of a pandemic virus and is designed to confer protection against it. The vaccine contains viral antigens to which humans are immunologically naïve and which therefore necessarily differ from antigens used in seasonal vaccines. A dossier for this pandemic-like vaccine (including data on antigen content, immunogenicity, safety, and efficacy) is submitted for provisional regulatory approval prior to the start of a pandemic. When a pandemic virus emerges, a variation to the dossier, with technical data specific to the pandemic virus, is then submitted for final marketing authorization.

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