CHIRON

Statement Presented To

Committee on Government Reform

United States House of Representatives

By Howard Pien

President and CEO

Chiron Corporation

February 12, 2004

Introduction
Mr. Chairman, Members of the Committee: Thank you for the opportunity to provide a statement to the House Government Reform Committee at today's hearing. I am Howard Pien, president and CEO of Chiron Corporation, a global biotechnology company headquartered in Emeryville, California. Chiron Corporation, founded in California in 1981, is composed of three business units: BioPharmaceuticals, Blood Testing and Vaccines. Chiron is dedicated to research and innovation addressing global public health challenges. Through Chiron's breakthrough research discoveries in the fields of hepatitis B virus, human immunodeficiency virus and hepatitis C virus, millions of potentially fatal infections have been prevented.

Overview of Chiron
Chiron is the fifth-largest vaccines producer in the world, with sales of $678 million in 2003. Chiron Vaccines produces pediatric and adult vaccines to prevent life-threatening illnesses. These vaccines, which are sold throughout the world, have protected millions of people globally from *N. Meningitidis* Group C, polio, measles and other potentially fatal diseases. Chiron is a leading supplier of oral polio vaccine, producing more than 800 million doses annually to support global polio eradication efforts. Our rich heritage in vaccines is traced to the three European manufacturers Chiron has acquired over the past two decades, all of which were founded 100 years ago or more. The company has production facilities in Liverpool, United Kingdom; Siena, Italy; Marburg, Germany; and Ankleshwar, India; and it carries out research in Siena, Marburg and Emeryville. Chiron has a successful record of product development, including the launch of the first recombinant vaccine against pertussis, the first adjuvanted influenza vaccine and a conjugate vaccine against *N. Meningitidis* Group C.

Chiron currently has two vaccines licensed in the United States: Fluvirin® flu vaccine, one of only two injectable influenza vaccines approved by the U.S. Food and Drug Administration, and RabAvert® rabies vaccine, approved by the FDA in 1997. Chiron also supplies diphtheria and tetanus (DT) concentrate to GlaxoSmithKline for use in its DT-containing vaccines licensed by the FDA.[1] In addition, Chiron has initiated Phase III studies in the United States with the aim of licensing its conjugate vaccine against *N. Meningitidis* Group C, Menjugate®.[2]

Chiron and Influenza Vaccines
Chiron Corporation's $878 million acquisition of PowderJect Pharmaceuticals and its influenza vaccine Fluvirin in July 2003 represents a major commitment to ensuring that an adequate supply of vaccine is available to meet the needs of the United States. The principle driver for the acquisition was Fluvirin, which is produced at the company's FDA-approved and FDA-licensed facility in Liverpool. Approximately 90 percent of the production from the facility is delivered to the United States, with most of the remainder going to the United Kingdom.

Prior to its acquisition of PowderJect, Chiron was the third-largest producer of influenza vaccines globally and the second-largest supplier of influenza vaccine outside the United States. Today, Chiron is the second-largest producer of influenza

[1] Infanrix (DtaP) & Pediarix (DtaP-HepB-IPV)
[2] Menjugate® has been licensed in Europe via the Mutual Recognition Procedure and is also approved in other countries, including Canada and Australia.

vaccines in the world, with production of approximately 75 million doses annually. Chiron produces influenza vaccines at its facilities in Liverpool, Marburg and Siena and offers a number of influenza vaccines.

Currently, all influenza vaccines marketed in the United States are produced in embryonated hens' eggs from designated chicken flocks. Individual lots of each of the three virus strains are grown in the eggs and harvested. The harvested virus is inactivated (killed), purified and separated from the egg proteins, usually by high-speed ultra-centrifugation. The whole virus concentrates are then further purified and split (split vaccine) or purified, as for Fluvirin, such that the vaccine contains predominately only the hemagglutinin and neuraminidase virus coat proteins (surface antigen or sub-unit). The monovalent (single-strain) antigen lots are then sterile-filtered and Quality Control and potency tested. The monovalent lots are then formulated into trivalent vaccine (following FDA release), filled into the final containers and packed. The final run of primary antigen production in eggs is usually completed by September to allow time for processing, FDA potency assignment, vaccine formulation, packaging, QA release and shipping to have completed release of the product into the marketplace by October or November.

In addition to its conventional egg-based influenza vaccines, Chiron is pursuing development of a cell culture–based subunit influenza vaccine using the Madin-Darby Canine Kidney (MDCK) cell line. Chiron's influenza cell-culture research program has completed Phase II clinical trials, with licensure in Europe projected sometime during the latter half of the decade. A Chiron influenza cell-culture production facility for full-scale production of the vaccine exists in Marburg. Chiron has initiated discussions with the FDA and plans to submit an Investigational New Drug Application to pursue licensure of an influenza cell-culture vaccine in the United States.

While there do not appear to be significant clinical advantages to cell-culture vaccines as compared with the current egg-based vaccines in terms of safety and efficacy, the cell-culture production process offers several potential advantages. The overall process is more flexible and can be more easily adapted to increases in market demand. Additionally, the fermentation process is highly compliant with Good Manufacturing Practice (GMP) compliance.

In the event of an influenza pandemic, the cell-culture production process could offer significant benefits compared with the conventional process, including:

- Increased production capacity via faster initiation of continuous manufacture.
- Lack of dependence on a supply of eggs, which could be a key rate-limiting step in meeting an urgent public health crisis. Production can start at any time and can easily be expanded to full-year production.
- Reduction of production lead-time by six to eight weeks.
- Cell-culture production, unlike egg-based production, is a closed process that can be easily upgraded to Class III bio-safety standards that may be required for the management of a pandemic strain.
- Cell-culture production is suited to producing vaccines for influenza of avian origin, which will not grow on eggs without genetic modification.

Overview of Egg-Based Influenza Vaccine Production

Influenza vaccine usually contains three different influenza strains that are recommended by the World Health Organization (WHO) and FDA. The strains are selected to match the families of influenza viruses expected to be circulating each winter, following WHO continuous surveillance. The vaccine has a new composition each year, and the vaccine therefore cannot be stockpiled but must be made to order each year. In addition, influenza vaccine is a seasonal product, with the majority of immunizations occurring in the September-to-November time frame in the United States. If there is surplus vaccine that is unused at the end of the season, it cannot be reused the following year and must therefore be destroyed. The requirement for Southern Hemisphere influenza vaccine in the January to March season is comparatively small and usually of a different composition.

Vaccine manufacturers try to match annual supply and demand, ensuring enough doses are available to meet demand while avoiding wasteful destruction of unused vaccine at the end of the season. The inability to carry over inventory into the following season means that the margin of error is much smaller than for other vaccines. Forecasting demand accurately is complicated by the fact that it is not possible to assess the severity of the epidemic and then adjust production volumes; additional capacity cannot be added at short notice and must be planned at least one season in advance. The cycle time for vaccine production means that demand must be predicted based on historical data, without an indication of the severity of the current influenza epidemic.

Supply of Influenza Vaccine in Interpandemic Years

It is important to put the 2003 influenza season and the resulting demand for influenza vaccine into perspective by comparing it with previous years in which the influenza epidemic was less severe. In 2003, all supplies of injectable influenza vaccine produced for the United States appear to have been used, resulting in an estimated 83 million Americans being immunized against influenza. A milestone was reached: The estimated 83 million Americans immunized represent the highest immunization rate ever for influenza. Prior to 2003, immunization rates had remained relatively static, and unused vaccine had to be destroyed. For example, it is estimated that approximately 12 million doses were destroyed in 2002. It seems safe to assume, given the severity of the epidemic and the publicity in the media in 2003, that more people would have been immunized had additional supplies of influenza vaccine been available. Therefore, it is not surprising that the focus has been on the shortage of vaccine that occurred and how to prevent its occurrence in the future rather than the victory in reaching this public health milestone.

While one cannot underestimate the potential severity and impact of an influenza pandemic on the United States, ensuring an adequate supply of vaccine and achieving high immunization rates in interpandemic years is of major importance from a public health perspective. Influenza pandemics are irregular events occurring infrequently, approximately once every few decades. The influenza epidemic is an annual event, which was estimated during the 1990s to have caused an average of approximately 36,000 deaths per year[3] and 114,000 hospitalizations in the United States. This represents a significant burden of disease even when compared to the impact of a

[3] Source: Morbidity & Mortality Weekly Report 2003, Vol. 52 RR8

pandemic. It is estimated that approximately 500,000 deaths due to influenza occurred in the United States between September 1918 and April 1919 and that the pandemic caused 20 million deaths worldwide. The 1918–1919 pandemic was the worst pandemic recorded, and mortality in more recent pandemics has been lower. The Asian influenza pandemic of 1957 is estimated to have caused approximately seventy thousands deaths in the United States while the Hong Kong influenza pandemic of 1968 is estimated to have caused 33,000 deaths.[4] Therefore, while pandemic preparedness is crucial from a public health perspective, the public health benefits of implementing a routine influenza immunization program in interpandemic years should not be underestimated. Not only would it help prepare the United States in the event of a pandemic by ensuring that production capacity and mechanisms for distribution and delivery of vaccine are in place, but it also would reduce the annual burden of disease and death due to influenza.

The following must be in place in order to minimize the burden of disease caused by the annual influenza epidemic:

- An adequate supply of influenza vaccine in non-pandemic seasons to protect the population.
- Appropriate mechanisms to ensure delivery of the vaccine to the target populations.
- High public awareness on the need for immunization to ensure use of the vaccine by the target population.

Prior to its acquisition of PowderJect, Chiron was not committed to entering the U.S. influenza market for economic reasons. However, over the last few years, significant changes in the dynamics of the U.S. influenza market have occurred. The key changes are:

- The recommendations of the Advisory Committee on Immunization Practices (ACIP) on influenza immunization were broadened to include individuals between 50 and 64 years of age and healthy children between 6 and 23 months of age, significantly expanding the potential market for influenza vaccine.
- Pricing of influenza vaccines has reached a level that allows manufacturers to invest in maintaining facilities to meet FDA standards and in expanding manufacturing capacity in order to meet the increased demand.
- Reimbursement rates for providing influenza injections have been increased to levels at which physicians are encouraged to actively immunize patients.

These changes in market dynamics were key factors in Chiron's decision to acquire PowderJect and expand its strong presence in the influenza market to include the United States. There has been considerable comment in the media about the decision of three influenza vaccine manufacturers to discontinue production over the past few years and the resulting decrease in supply. However, it should be noted that two of the producers exited at a time when the market price of the vaccine was significantly lower, making it difficult to justify the investment required to maintain facilities to FDA standards or to consider an increase in capacity. The changes in market conditions over the past few years have resulted in a reduction in the barriers to investment, and the impact of these changes are beginning to be felt.

[4] Source: www.cdc.gov/od/nvpo/pandemics

The shift in dynamics has had a significant impact on investment decisions and capacity at Chiron. Over the past five years, investments of approximately $70 million in both primary (bulk) and secondary (fill/finish) manufacturing have been made to increase the production capacity of the Liverpool facility. This investment has resulted in a significant increase in the amount of Fluvirin supplied to the United States: The amount of Fluvirin supplied to the United States on an annual basis more than tripled from 12 million doses in 2000 to 38 million doses in 2003. Additional increases in production capacity and, consequently, to supply to the United States are planned for 2004 and beyond. Chiron is projecting that it will be able to produce approximately 50 million doses of Fluvirin in 2004, with the vast majority destined for the United States. If sufficient demand for influenza vaccine exists, Chiron plans to increase its production capacity and supply of influenza vaccine to the United States even further beyond 2004.

Building on recent investments to increase manufacturing capacity at the Liverpool facility, Chiron is committing an additional $100 million dollars to replace the existing influenza bulk manufacturing facility in Liverpool with a new "state of the art" facility[5] to complement the secondary manufacturing facility opened in 1998. This commitment is being made to ensure that Chiron is in a position to continue to supply Fluvirin to the United States and to add incremental capacity until the FDA approves its cell-culture vaccine and sufficient cell-culture production capacity is available to meet the market needs in the United States.

It should be recognized that changes in market dynamics, specifically the increase in price that has occurred over the past three years, have reversed the trend of decreasing manufacturing capacity as producers are investing in capacity increases and upgrading facilities and licensing cutting-edge technologies for the U.S. market. Chiron manufacturing investments are not unique to the industry, suggesting that the growing U.S. influenza market is an important public health priority that the private sector must ensure is met. However, given the nature of biologics manufacturing there is inevitably a lag between the decision to invest and improved capacity as a result of that investment. The United States is only now beginning to see the impact of the positive changes in market dynamics that occurred a few years ago with regard to expanded investment in manufacturing capacity.

The early onset of the 2003 influenza season and the resultant increase in demand above levels seen in previous influenza epidemics created a shortage of vaccine which has led to concerns in the media and general population about the fragility of influenza vaccine supply and its potential impact on the health of the U.S. population. However, the influenza vaccine supply situation is much less fragile than for many other commonly used vaccines in the United States. The recent Institute of Medicine Report "Financing of Vaccines in the 21st Century Assuring Access and Availability"[6] highlighted the fact that a single source of supply existed for six of the recommended vaccines[7] in the United States. This means that no backup capacity is available should a manufacturer experience production problems or other disruptions creating a

[5] A new fill/finish facility was completed a few years ago.
[6] Institute of Medicine, August 2003
[7] Tetanus-diphtheria, measles-mumps-rubella, varicella (chicken pox), pneumococcal conjugate, meningococcal polysaccharide, pneumococcal polysaccharide

significant potential for supply interruptions. Indeed, these have occurred over the past few years. In 2001 and 2002, eight of the 11 recommended childhood vaccines were in short supply.[8] These shortages impacted immunization policy in the United States, forcing the ACIP to temporarily revise its recommendations on pneumococcal conjugate vaccine and diphtheria, tetanus and pertussis (DtaP) and to recommend that varicella (chicken pox) immunization be pushed back to 18-24 months from 12-18 months. In contrast, there are now three sources of supply for influenza vaccine, making a complete disruption of supply an unlikely event.

Key public policies are of critical importance to ensure that influenza production in interpandemic years is adequate. A competitive environment that encourages multiple suppliers of vaccines to ensure continuity of supply is vital. Implementation of any public purchase program with a "winner take all" approach could have the unintended impact of discouraging potential suppliers by increasing the risk associated with participating in the market, as production is impossible to plan in an "all or nothing" situation.

The shortage of vaccine in 2003 has led to a tremendous focus on the supply side of the equation and mechanisms for increasing supply to meet an above-ordinary level of demand. A key lesson learned was that demand for influenza vaccine in a severe epidemic can reach levels above those anticipated for a more typical season and that producers are not able to adjust supply to meet the surge in demand once the season has started. The production cycle times for influenza vaccine are such that by the time the surge is identified it is too late to increase supply to meet the increase in demand. This has led to proposals aimed at ensuring a sufficient supply of influenza vaccine for the United States in the event a severe epidemic leads to a surge in demand. Many of the proposals involve mechanisms guaranteeing purchase of influenza vaccine by the federal government with a primary objective of creating a strategic reserve to meet an above-average level of demand for influenza vaccine. Essentially, the purpose of these purchases would be to provide insurance against a severe epidemic by encouraging manufacturers to expand capacity to produce volumes above predicted levels of demand in the event of a typical epidemic. The premise of the mechanism would be to transfer the risk of investing and carrying excess inventory from the producers to the federal government.

As Congress and the Administration consider these proposals, Chiron is committed to working collaboratively with you to craft balanced solutions. Together we must fully consider issues relative to the timing of implementing new approaches to supply, opportunities to expand immunization rates to meet the Healthy People 2010 objectives, and the potential risk to existing supply and distribution channels. Chiron's perspective is as follows:

- Chiron is prepared to increase its supply of influenza vaccine by extending the production season and delivering additional doses in late November and December. At present, Chiron does not do this, as U.S. demand for influenza vaccine after November does not usually occur. Based upon U.S. immunization trends prior to 2003, extension of the production season heretofore would have led to unused vaccine that would have ultimately been destroyed.

[8] USA Today, February 18, 2002

- The go/no-go decision on whether to extend the production season needs to be made early in the year to guarantee the supply of eggs required for vaccine production. Therefore, a commitment to purchase the doses would need to be made prior to this date, when no real indication of the severity of the epidemic exists. Theoretically, a go/no-go decision on extending the production season could be made in June. However, a concern exists regarding reliability of egg supply, and this would not be the optimal solution on an ongoing basis.
- In order to maximize the benefit of the program, guaranteed purchase of vaccine should be distributed among all suppliers who are able to provide vaccine.
- Demand created by these purchases would be artificial if not accompanied by an increase in vaccinations, as the incremental doses would be destroyed at the end of the season. While the primary intention of these purchases is to create a buffer to meet unanticipated surges in demand, concerns exist about the long-term viability of any purchase program where doses would be destroyed. Essentially, the program would achieve its goals in the short term, but Chiron believes that real demand for influenza vaccine must be increased if supply is to grow in the long term.
- Any expansion of government programs for the purchase influenza vaccine beyond existing programs, such as Vaccines for Children and 317 funds, should contain components to ensure expanded use of the vaccine in order to prevent destruction of unused doses at the end of the season, which could detrimentally impact the demand side of the equation.
- Government involvement, while it may be appropriate and necessary, may have unintended consequences that we need to be cognizant of and manage prospectively. Large-scale government purchases of vaccine have the potential of disrupting the current private-sector distribution system for influenza vaccines.

We believe that the factors highlighted above can be effectively managed in a prospective fashion by collaboratively developing a program to secure a strategic reserve by the government that does not create the unintended consequences or detrimentally impact the private market.

Ensuring increasing year-on-year demand for influenza vaccine under routine circumstances creates a market-efficient solution to the issue of meeting episodic surges in demand, as it prospectively balances supply and demand in the event of a severe epidemic. Furthermore, focusing on solutions impacting the demand side of the equation is important in the context of planned increased production capacity for future seasons. If demand remains static or returns to levels seen in 2002, a situation will exist where demand exceeds supply. As mentioned previously, 2003 represented the highest number of people ever immunized, and there is no guarantee that the same levels will be achieved in the event of a less severe epidemic.

Chiron's concern is that in future, if demand remains static, the United States will return to a situation where supply will again exceed demand, leading to unused vaccine doses being destroyed, as has occurred in the past. This would trigger a reassessment by Chiron of the need to increase influenza supply and, depending on any demand shortfall, may even lead to a reduction in supply in future years. We

should therefore not be complacent and assume that because excess demand existed in 2003, it will automatically spill over to future years and absorb projected supply for the U.S. market.

In order to raise influenza immunization coverage rates to effectively use the additional supply that will be available next year, key stakeholders (manufacturers, distributors, the public health community, providers and insurers) should collaborate on the following issues:

- Raising awareness of the immunization recommendations among the medical community and general population.
- Encouraging immunization by highlighting the benefits of immunization and developing innovative programs for facilitating access to the vaccine.
- Extending the immunization season into December to ensure all doses are used and to potentially increase the window in which vaccine could be supplied to the market.
- Creating an environment that supports manufacturers who produce doses at risk.

Furthermore, these efforts must not be limited to the 2004 season but must be continued for the long term. A significant increase in demand for influenza vaccine is required to achieve the Healthy People 2010 goals of 90 percent coverage rates of non-institutionalized adults 65 years of age and older and 60 percent coverage rates of high-risk non-institutionalized adults 18-64 years of age.[9] While these goals are ambitious, they are achievable if both the public and private sector collaborate on achieving them. The success of such partnerships in raising immunization rates for pediatric vaccines demonstrates how this approach can achieve positive results. It is recognized that there are differences between influenza vaccination and the pediatric immunization situation, where school entry mandates played an important role in raising coverage rates. Nevertheless, it is felt that some of the lessons learned would be applicable.

In conclusion, Chiron believes the building blocks are in place to ensure a reliable supply of influenza vaccine for the United States in interpandemic years because:

- The pricing environment has reached levels where it supports manufacturers' investment in production capacity for the United States, as evidenced by the investments made by Chiron and other producers in recent years. The results of these investments are beginning to be realized.
- Federal recommendations expanding significantly the number of individuals eligible for the vaccine are in place and production capacity is being increased to meet these targets.

Chiron believes that the main challenge moving forward will be ensuring that demand continues for the capacity that it projects will come on stream over the next few years. Based on the success of initiatives in raising pediatric immunization rates, it is believed that partnerships between key immunization stakeholders in the private and public sector represent the best option for increasing demand. Chiron wishes to partner with stakeholders and is prepared to invest resources in efforts aimed at

[9] The target rate for institutionalized adults aged 18 and older is 90 percent.

increasing immunization coverage. Finally, while Chiron believes guaranteed purchase of influenza vaccine by the federal government could provide a short-term solution to meeting above average demand in the event of a severe epidemic, provided incentives are properly structured, it is concerned about the long-term viability of any program that would artificially raise demand and result in surplus doses of vaccine being destroyed. Chiron therefore believes that focusing on increasing demand on an annual basis, thereby reducing the level of unexpected demand in the event of a severe epidemic, might provide a more viable long-term alternative. Chiron welcomes the opportunity to provide input into proposals as they are being developed.

As stated in a recent editorial in the New England Journal of Medicine:

> "Ultimately the experience of 2003-2004 may help us deal with influenza epidemics more effectively. The public awareness and media attention that accompanied reports of severe illness in children have resulted in greater recognition of both the severity of influenza in all age groups and the benefits of influenza vaccine. This recognition may spur increased use of vaccination and help us achieve the goals for vaccine coverage encompassed by the Healthy People 2010 Initiative. Increased demand for vaccine will encourage manufacturers to continue producing it, possibly in greater quantities. Increased production is critical toward developing the surge capacity that will be needed to deal with new pandemic viruses when they occur."[10]

U.S. Influenza Supply in a Pandemic

The impact of an influenza pandemic would not be limited to the United States, as the entire global population of 6 billion people would be at risk. The global nature of a pandemic presents a significant challenge to the public health infrastructure and to influenza vaccine manufacturers in particular. Chiron is committed to supporting pandemic preparedness efforts and is actively involved in pandemic preparedness working groups at both the international and national level:

- At the international level, Chiron co-sponsors a specialized group of influenza vaccine manufacturers, the Influenza Vaccine Supply Task Force (IVS TF), created in 2001 with the endorsement of the International Federation of Pharmaceutical Manufacturers Associations. The group is made up of 11 companies representing 80 percent of total global influenza vaccine production capacity. The IVS TF is providing industry input on pandemic preparedness planning to bodies such as the WHO, European Commission, European Medicines Evaluation Agency (EMEA), and other international, national and local health authorities.
- At the European level, Chiron, together with other influenza vaccine manufacturers represented by the European Vaccine Manufacturers (EVM) group, is directly involved in many activities regarding pandemic preparedness in Europe.
- Chiron submitted a pandemic capability statement in June 2003 at the request of the U.S. Centers for Disease Control and Prevention (CDC) and the National Vaccine Program Office (NVPO).

[10] Treanor, J., New England Journal of Medicine, January 15, 2004.

From the perspective of an influenza vaccine producer, planning for a pandemic represents a significant challenge due to the nature of the product being manufactured. Essentially, the following factors limit the ability to rapidly expand supply in the face of a pandemic under current circumstances:

- **Production capacity**—Influenza vaccine production capacity is aligned with annual demand for vaccine under normal circumstances, i.e., between pandemics, and therefore little or no surge capacity exists to meet pandemic demand.
- **Inability to stockpile**—Stockpiling of vaccine in preparation for a pandemic is not a viable strategy, as it is not possible to predict the vaccine strain that will cause the pandemic.
- **Supply of primary production material**—Currently, vaccines are produced using eggs, and ensuring an adequate supply of eggs to significantly increase production during a pandemic represents a significant challenge.
- **Specialized production facilities**—Additional quantities of vaccine could not be readily produced in facilities used for other vaccines, as production and purification equipment and facilities are specifically designed for influenza vaccines.

Chiron has plans to maximize production of influenza vaccine at its Liverpool, Marburg and Siena facilities to help overcome these challenges in the event of a pandemic. The following steps would be undertaken to increase vaccine production:

- **Year-round production**—Influenza vaccine production would be run continuously over the whole year as opposed to the current seasonal production cycle. However, it should be noted that this assumes that additional egg supply will be available to keep the facilities running year round.
- **Monovalent vaccine**—A monovalent vaccine containing the pandemic strain only would be produced as opposed to the standard trivalent vaccine containing three strains. Manufacturing capacity would therefore be increased by a factor of three, assuming that the vaccine contains the same amount of antigen as the conventional influenza vaccine.[11] Any increase in the antigen content of the pandemic vaccine would result in a proportional reduction in the number of doses that could be produced. At present, the clinical data available to support the definition of the pandemic vaccine is limited.

Chiron estimates that implementing these two steps in the event of a pandemic would more than triple its influenza vaccine manufacturing capacity, of which 50 percent would be produced at its FDA-licensed facility in Liverpool, assuming the pandemic vaccine contains the same amount of antigen as the normal vaccine. By the end of the decade, under its current plan, Chiron anticipates being able to increase its pandemic vaccine production by an additional 50 percent due to expanded production capacity in Liverpool and the availability of a cell-culture facility in Marburg producing its MDCK–based cell-culture vaccine.

[11] It should be noted that studies of experimental vaccines produced in response to the avian influenza A outbreaks in Hong Kong suggest that a greater dosage or an adjuvanted vaccine may be required. Therefore, whether this assumption will turn out to be valid is open to question.

Adjuvantation[12] of the pandemic vaccine could theoretically expand production capacity even further by reducing the required antigen dose. However, limited clinical data for the pandemic strain situation exist. Chiron therefore believes that it would be of significant benefit if publicly funded studies were undertaken with a goal of defining the characteristics (e.g., antigen and/or adjuvant dose) of a "pandemic-like" vaccine and vaccination schedule.

A pandemic would not represent a "business-as-usual" situation for Chiron. Implementing these steps to increase influenza vaccine production would occur at a cost of using resources normally devoted to the production of other vaccines. For example, producing the additional influenza vaccine would take up additional filling capacity impacting the ability to fill other vaccines. Therefore, production of the pandemic vaccine would potentially disrupt Chiron's ability to supply other vaccines to its customers. This disruption in supply could lead to public health consequences if alternative sources of supply could not be found or adequate stockpiles were not in place. At present, the impact of disruption of supply on the United States would be limited, as the only Chiron vaccine that could be impacted is its rabies vaccine. However, global markets for Chiron's pediatric and adult vaccines would be detrimentally impacted.

In the face of a potential influenza pandemic, switching production to a monovalent pandemic vaccine imposes a significant financial risk: If the predicted pandemic failed to materialize, there would be no demand for the monovalent vaccine, and Chiron would be forced to destroy the vaccine. Therefore, Chiron would be unlikely to make the decision to switch production from trivalent vaccine to a monovalent pandemic strain without a guarantee that its production would be purchased whether or not the pandemic materialized. Chiron would be unable to assume this risk without financial guarantees being in place due to the severe consequences of losing an entire year's revenues generated from the production of influenza vaccine. Therefore, in order to trigger a switch to pandemic vaccine production as quickly as possible in the event of a potential pandemic, governmental guarantees to purchase the vaccine and an agreed-upon purchase mechanism should be in place. The need for a mechanism to guarantee purchase implies a limited role for the private sector in the marketing of a vaccine in the event of a pandemic. National governments will procure the vaccine, be responsible for its distribution and determine the priority of immunization. Based on these considerations, Chiron assumes that in the event of a pandemic, the market for influenza vaccine will be almost exclusively a public-sector market, with national governments purchasing vaccine from producers. In addition, Chiron assumes a mechanism for indemnifying manufacturers, similar to that of smallpox, will be in place.

It is important to note that the current regulatory approval process would have to be expedited in order for manufacturers to rapidly convert to producing a monovalent pandemic vaccine in a timely fashion. Under the present system, obtaining regulatory approval could be a bottleneck in supplying pandemic vaccine. Chiron believes that discussions and planning should occur now between manufacturers and the FDA in

[12] Adding an adjuvant, a substance that improves the immune response to the vaccine.

order to determine the regulatory pathway for approval of a vaccine, including any amendments to official release requirements in the event of a pandemic. This would be of significant value to expedite the availability of supply should the pandemic occur.

Despite a potential increase in the supply of vaccine by a factor of greater than three, there will be a global shortage of influenza vaccine in the event of a pandemic. Demand for influenza vaccine would increase dramatically compared to normal circumstances due to the need to immunize most of the global population and a potential increase in the number of doses required per person to provide immune protection from one to two. Current global influenza vaccine production capacity, estimated at roughly 300 million doses in a typical year,[13] will most likely be unable to cope with global demand, and therefore a shortage of vaccine is expected to occur.

Chiron is committed to maintaining supply to the United States in the event of a pandemic. However the current location of Chiron's influenza manufacturing facilities outside of the United States imposes constraints on its ability to ensure this occurs, as it is not clear how global allocation of the vaccine will take place in the event of a pandemic. Where demand outstrips supply, it is possible that national authorities will impose constraints on the allocation of influenza vaccine by manufacturers under their jurisdiction. One of the constraints that may be imposed by national authorities is that producers be required to give priority to meeting national demand before shipping vaccine supply to traditional markets. For example, Chiron could be asked to give precedence to the United Kingdom in allocating vaccine supply from its Liverpool facility, as it is the only domestic source of supply for that country. Furthermore, once the needs of the United Kingdom were met, priority might be given to other European countries before allowing vaccine to be made available to the rest of the world. In addition, manufacturers with facilities located in European Union countries may be required by their national authorities to give precedence to the needs of other EU member countries once domestic needs have been met before vaccine can be exported outside of the EU, particularly for those member states that do no not have domestic production capacity. These variables are real and uncharted.

A critical success factor to pandemic preparedness efforts in the United States would therefore be increasing domestic production capacity of influenza vaccine in order to ensure a supply of vaccine free from external pressure in a pandemic. Ideally, this would involve creating new facilities rather than expanding capacity at the only domestic facility because, as stated previously, reliance on a single supplier is inherently risky.

If new facilities were to be built in the United States with a primary objective of ensuring supply of vaccine in the event of a pandemic they should be based on cell-culture technology as opposed to the current egg-based production. Cell-culture technology offers significant advantages in the event of a pandemic as previously highlighted in this statement. The private sector appears to represent the best option for expediting the availability of domestic cell-culture production capacity as access to a scaled-up production process would considerably shorten development timelines.

[13] Chiron internal estimate.

Chiron has yet to decide whether it will expand its planned cell-culture production capacity in Marburg in order to supply the U.S. market, but several potential scenarios for capacity expansion have been evaluated. These involve either increasing production at the Marburg site or developing a "green field" site in Europe, the United States or elsewhere for the production of influenza cell-culture vaccine. The decision as to which approach to take will primarily be based on financial considerations, such as the required level of capital investment and Chiron's ability to expeditiously commercialize influenza cell culture. A preliminary analysis suggests that capacity expansion at Marburg could be the fastest and probably most cost-effective option for Chiron due to the benefits of economies of scale in concentrating production at a single site. Developing a new facility on a "green field" site capable of producing 50-70 million doses of conventional trivalent influenza cell-culture vaccine and more than 200 million doses of monovalent pandemic vaccine is estimated to require a capital investment or more than $200 million.

To expedite pandemic preparedness, Chiron believes that the United States should consider providing incentives, such as tax relief or a contract to guarantee purchase of a certain volume of vaccine at a specified rate, to encourage influenza vaccine producers to locate cell-culture production facilities in the United States. The objective of these incentives would be to ensure that in a pandemic situation the United States has access to cell-culture influenza vaccine free from external government jurisdiction. These incentives should be structured to result in more than one production facility being developed so as to avoid reliance on a single supplier. Incentives should be structured to encourage the location of "bricks and mortar" in the United States as opposed to encouraging the development of a cell-culture vaccine. Financing the development of a vaccine may expedite licensure of a new product or products but would not guarantee that the source of supply will be located in the United States, a key objective for pandemic preparedness. Chiron believes that the private sector is best placed to rapidly bring these facilities on stream as vaccine producers have access to scaled up cell-culture manufacturing processes from production facilities located outside of the United States, which could easily be transferred to a new plant.

In conclusion, an influenza pandemic will represent a significant challenge to Chiron, as it will need to rapidly expand influenza vaccine at the expense of other products in its portfolio. Recognizing this challenge, Chiron is committed to supporting global pandemic preparedness efforts prior to the inevitable occurrence of a pandemic. Chiron believes that continuing to forge partnerships between vaccine manufacturers and the public health authorities is crucial in order to discuss and resolve the following issues:

- Increasing demand during interpandemic years to encourage increased capacity.
- Determining whether or not pandemic vaccine supply can be expanded by adjuvantation of the vaccine.
- Identifying the regulatory pathway for approval of a pandemic vaccine, including any amendments to official release requirements in the event of a pandemic.
- Establishing a mechanism to indemnify influenza manufacturers.

- Implementing mechanisms to trigger the switch to production of a monovalent pandemic vaccine through guarantees to purchase output whether or not the pandemic materializes.
- Incentivizing U.S. influenza manufacturing capacity.

In summary, Chiron has invested heavily in ensuring that the United States has a supply of influenza vaccine in interpandemic years. Chiron is committed to providing leadership in the U.S. influenza market. Chiron is shouldering the necessary risks to expand its ability to increase supply and is bringing cutting-edge technologies in influenza cell-culture production to the U.S. market. Fundamental to Chiron's success in realizing its commitments is the ability to work collaboratively with Congress, the Administration and public health officials to reach the immunization rates established in Healthy People 2010 while incentivizing the private sector to transition to new technologies in influenza immunization. These priorities are of critical importance if we are to effectively position the United States for preparedness for a global influenza pandemic.

Thank you for the opportunity to present the views of Chiron Corporation. I am happy to answer any questions you may have for me.