

Risk Factors

Our Management Board is responsible for designing, implementing and operating the Company's internal risk management and control systems. The purpose of these systems is to manage in an effective and efficient manner the significant risks to which the Company is exposed. For a more detailed description please see 'Internal risk management and control system' in the Corporate Governance section of this Annual Report.

An integral part of our internal risk management process is the identification of risks that could prevent us from reaching our objectives. To identify these risks we performed a corporate risk assessment with the Disclosure Committee of the Company in 2008. The outcome has been discussed in the Audit Committee and was taken into account in the risk factors described below. We have classified these risk factors in accordance with the categories of objectives identified in the COSO model, an integrated internal control framework established by the Committee of Sponsoring Organizations of the Treadway Commission.

You should carefully consider these material risk factors. The risks we face are not limited to the risks listed here. Some risks are not yet known to us and some of the risks that we currently do not believe to be material to our operations could prove to be material at a later date. All of these risks can materially affect our business, financial condition and results of operations.

Strategic

Concentration of sales

We are dependent on a limited number of products and customers for a majority of our revenues and expect this dependence to continue in the foreseeable future. Our core product portfolio consists of seven vaccines, namely Quinvaxem, Hepavax-Gene and MoRu-Viraten (paediatric vaccines), Inflexal V (influenza), Dukoral, Epaxal and Vivotif (travel vaccines). The aggregated revenues for our core product portfolio represented a significant part of our total product sales in 2008. The sales to our largest customers, which are in the paediatric vaccines area, represented a considerable part of our net product sales in 2008. In particular, we are highly dependent on sales of Quinvaxem and Inflexal V. If these products were to become subject to any problem such as unexpected side effects, product liability litigation, loss of patent protection, supply interruptions, regulatory proceedings,

publicity affecting doctor or patient confidence or pressure from competitive products, or if a new more effective treatment is introduced, we could experience a significant decrease in revenues and an adverse effect on our financial results.

Additionally, our results may fluctuate as a result of seasonality in our business. In particular, the market for flu vaccines is highly seasonal so a majority of our distribution and sales tends to occur in the second half of the year. Delays in any step of our regulatory approval, production or distribution processes could result in a significant sales reduction.

Strategic alliances

If our current or prospective partners or licensees do not use our products or technologies, we may not be able to continue to realize revenues related to those partners or licensees. In particular, our current or prospective licensees or partners may use or develop alternative technologies or competing products, independently or in collaboration with others, including our competitors. If any of our licensees or partners becomes involved in a business combination or other major corporate transaction, this could cause a strategic shift in their business focus and lead them to discontinue the use of our products and technologies.

Furthermore, we may have disagreements with our licensees over royalty payments owed to us and may have difficulty collecting these payments. Our existing license arrangements generally entitle us to receive royalty payments for any products developed using our technology. We depend on our licensees to inform us when they develop products using our technology. If our licensees fail to inform us of these developments, we may not otherwise learn of payments to which we are entitled. In addition, our licensees may have difficulties making payments to us given the current economic climate or other factors. We may also incur significant expenses in collecting royalty payments, or in some instances, may not succeed in collecting these payments at all.

Competition and pricing pressures

We face competition from other companies in the development, marketing and licensing of new technologies and products. We operate in competitive markets and compete with companies that have their own technologies, products or other forms of treatment for the diseases we target.

Companies may develop proprietary positions in the areas of our core technologies or obtain regulatory approval for alternative technologies or commercial products earlier than we or our licensees do. Other companies, including our own licensees, may already have or may in the future develop products that are more effective or more effectively marketed and sold than those based on our technologies. We may not be able to compete effectively with these companies, and such competition could hamper our ability to bring products to market or to license and derive revenue from our technologies.

Our existing products may experience pricing pressures from competition with other products on the market. Pricing pressures may further increase due to the introduction of new products, the expansion of production capacity, or decreases in demand. We cannot predict with accuracy the impact of such events on our revenues. Products that compete with Quinvaxem have already been introduced to the market and still others may yet be introduced. Increased competition from these products could result in further pricing pressure on Quinvaxem and a substantially negative impact on our revenues.

We experience pricing pressures in the public markets for our products, which typically operate via a tender system. In a tender system, national governments or supranational organizations request proposals for the terms under which a vaccine manufacturer will provide a large quantity of one or more vaccines. The awarding of the contract is typically based on a number of factors, including price, supply reliability and product quality. Failure to win one of these public contracts may cause us to be ineligible to supply a national government or supranational organization for a period of time, resulting in a negative impact on our revenues. Pricing pressures may have a material adverse effect on our business, results of operations and financial condition.

Operational

Product development and clinical trials

All of our products and those of our licensees and partners may fail at any stage of development or even after market introduction due to factors beyond our control. Such failures could have a material adverse effect on our business and prospects.

Pre-clinical testing, clinical research and regulatory approval of a pharmaceutical or medical product is a very lengthy and costly process, and there is a significant risk of failure at each stage of the process should issues arise with respect to the efficacy or safety of a product. In particular, because pre-clinical and early clinical studies cannot ensure efficacy for humans, actual human studies are required for vaccine development. Such studies may, however, fail to prove the efficacy of the product candidates and are at constant risk of suspension for posing unreasonable health risks. There can be no assurance that any product candidate in our product pipeline will reach or successfully complete the clinical research phase of product development. Although a product that reaches a later stage of development offers a reasonably high probability of success relative to products in earlier stages, the chances of failure remain significant throughout the development process. We have had products fail at later stages of development in the past. Any or all of our current later-stage products could fail to be shown sufficiently safe or effective to be brought to market, or could otherwise fail to receive necessary regulatory approvals.

Regulators have granted certain of our products provisional or conditional marketing approval, requiring us to do follow-up studies to assess the safety and efficacy of the product in all or part of the target population. Poor results in any of these studies may give rise to the withdrawal of market authorization for some or all indications, in part or in all of the targeted population. Even if the products currently in later-stage development are introduced to the market, there can be no assurance that demand for such products will develop or be sustained. If a market does develop, there can be no assurance that our existing facilities and resources will be sufficient to meet demand. Accordingly, there can be no assurance that we will realize any potential benefits that may be associated with our later-stage development product portfolio.

Our success depends on a sufficient pipeline of new products and technologies. We therefore commit substantial resources and efforts towards research and development. We have no assurance that these efforts will succeed. Failure to maintain a healthy flow of new products through our pipeline could result in higher costs without a proportional increase in revenues.

To a certain extent, we are dependent on third parties with whom we contract to perform clinical trials of our products. If we fail to adequately manage the work of these third parties, a regulatory authority may determine that they have not complied with applicable regulations and therefore may not approve a product candidate of ours.

To continue to develop our core technologies and new products, we will need access to biological materials such as virus and tissue samples, which may be in limited supply. If we lose or do not obtain access to these biological materials, or if tighter restrictions are imposed on their use or on the information generated from their study, we could be restricted or prevented from conducting certain research and product development.

Interrupted product supply

Supply interruptions, product recalls or inventory losses caused by unforeseen events such as manufacturing or distribution interruptions or regulatory actions, may reduce sales, delay the launch of new products and adversely affect our operating results and financial condition.

Our products are manufactured and distributed using technically complex processes requiring specialized facilities, highly specific raw materials and other production constraints. The complexity of these processes as well as strict Group and government standards for the manufacture of our products may expose us to risks affecting our production process. Defects in the manufacturing process, including equipment malfunction, labor problems, regulatory action, power outages, natural disasters and environmental factors may all affect production output. The new EU regulation (EC 1907/2006, REACH), requiring registration of all chemical materials by us and our suppliers, may cause supply interruptions of raw materials that may in turn cause production delays if we need to change our sources of certain raw materials or marketing delays due to new validation activities to demonstrate similarities, or differences in comparability studies between old and new suppliers. Our vaccine products in particular are subject to the risks of manufacturing problems and inventory loss because of the difficulties inherent in the manufacture of biological materials, whether in our own facilities or in the facilities of our suppliers. Vaccine components cannot be sterilized nor can preservatives be added to the manufactured vaccine. Contamination of our products could result

in the loss of entire batches of finished vaccine, which could lead to lost sales, damage to customer relations, a significant outlay of time and money to investigate the cause of the contamination and possibly a costly product recall if contaminated vaccines have already been shipped to customers. A disruption in the supply of certain key products or our failure to accurately predict the demand for those products could have a material adverse effect on our results.

We rely on a separate facility for the manufacture of each of our products. The marketing and regulatory authorization of biological products, in particular vaccines, is strongly linked to the production facility and equipment that are used to manufacture those products. If any event occurs that interrupts production at one of our facilities we may have to transfer production to a new site, which would be costly and time consuming. Because of the short shelf life of biological products, our existing stocks of product may not be sufficient to supply our customers during such a transition period. For example, our manufacturing facility in Korea is our sole production source of the Quinvaxem vaccine. As such, we are vulnerable to any event that interrupts, reduces or slows production of Quinvaxem at that facility. We intend to relocate our Quinvaxem operations to another site in Korea and preparations for such a move are ongoing. The relocation of the Quinvaxem operations is a complex process, which includes the inherent risk of the new facility not coming online before the old one has shut down. We agreed on the time line and conditions of this relocation with parties involved, enabling a smooth transition to the new production facility, however there can be no assurance that there will be no delay in the transition process.

We require a reliable supply of materials for the production of our products, including starting materials, like the serum-free medium in which we grow our PER.C6 cells, and antigens that are present in certain of our final products. Some of these materials are provided by a limited number of third party suppliers. Any interruption or termination of these supply relationships may have adverse effects on our ability to manufacture and sell products, particularly if we are unable to source new supplies of the same materials or adapt our technologies and manufacturing processes to use different starting materials in a timely manner. Our ability to conduct research and to launch new products also depends on a steady supply of these raw materials.

Any adverse changes to our existing supplier relationships will thus likely adversely affect our overall results.

Regulatory approval

We may be unable to obtain regulatory approval to manufacture and market our new products or may have regulatory approval for the manufacture and marketing of our existing products revoked by regulatory bodies such as the US Food and Drug Administration (FDA), the European Medicines Agency (EMA), the European Commission or other non-governmental bodies such as the World Health Organization (WHO).

These various regulatory authorities have substantial discretion and may impose different conditions upon the marketing of a given product or may refuse to grant, or require additional data before granting, an approval to market a product even though the product may have already been approved by another regulatory authority. National and regional governments rely on the (pre) qualification and/or approval of biopharmaceutical products by evaluative bodies such as the WHO and, in some cases, simply elect not to purchase products which have not been granted (pre) qualification or approval.

Once a product is approved, its manufacture and marketing remains subject to regulatory requirements including industry code of conduct regulations. Changes in applicable regulations, breaches of regulatory requirements or the discovery of problems related to the marketing, manufacture, safety, quality, efficacy or stability of a product, as well as changes in the characteristics of a manufactured product stemming from alterations in its biological origins, could result in the imposition of fines or restrictions upon the manufacture and sale of such product, including in the worst case scenario withdrawal of the product from the market altogether and/or the revocation of necessary regulatory approvals.

Regulatory requirements could make product development based on new technologies highly uncertain because regulatory review of the underlying technologies is generally required.

If regulatory authorities do not approve our new products or other products developed using our technologies, or if they subsequently revoke their approval, that may impact our revenues generated

from the sale of products and/or the licensing of our technologies, which may in turn have a material adverse impact on our business, financial condition, results of operations and prospects.

Intellectual property

Our efforts to protect our intellectual property rights or to defend ourselves against any claims of infringement of third party intellectual property may be costly and, if unsuccessful, we may be barred from using or licensing our technologies, and from developing and commercializing our new products.

Our commercial success depends in part on our ability to obtain and maintain adequate protection of our intellectual property rights, including patents, in our technologies and products in Europe, the US and elsewhere. Our patent-related activities do not afford complete protection to our intellectual property rights. Patents of technology-based enterprises like ours are subject to complex factual and legal issues that may give rise to uncertainty as to the validity, scope and priority of a particular patent. There can be no assurance that we will develop products that are patentable, that patents will be granted under pending or future applications or that patents granted to us or our collaborators will be of sufficient breadth to protect against competitors with similar technologies or products. A patent that is issued to us may be narrower than our application or found to be invalid. Others may make attempts to copy, reverse engineer or design around aspects of our technology, or to obtain and use information that we regard as proprietary. In addition, our patent filings may be subject to challenges. Our inability to adequately protect our products and technologies in emerging economies, such as India and China, may give rise to competition in those countries from manufacturers operating in low-cost economies. Due to compulsory licensing regimes currently in place in many of these underdeveloped and developing jurisdictions, we may not be able to use our intellectual property rights to prevent the low-cost manufacture of competing products. Such competition may adversely affect our ability to maintain viable pricing levels and to sell products in those countries.

In addition, production of Quinvaxem requires a particular vaccine component that may become the subject of a patent dispute between either GSK and us or GSK and our supplier of that component. The patent on that particular component, held by

GSK, is currently under opposition before the patent office and a definitive outcome on the validity of the patent is expected to take a number of years. A negative outcome of this opposition proceeding could lead to infringement proceedings between GSK and us or GSK and our supplier, although we believe that neither we nor our supplier would be held to have infringed or be infringing that patent. The outcome of legal disputes is invariably difficult to predict with accuracy, but in the event GSK were to prevail in infringement proceedings against us, this would adversely affect our business.

For a more detailed discussion of issues surrounding our patent enforcement and related proceedings, see 'Intellectual property – Patent enforcement and proceedings'.

We also endeavor to protect our proprietary technologies, processes, know-how and data by entering into confidentiality agreements with our employees, consultants, partners and certain contractors. We have no assurance that these agreements or other trade secret protections will provide meaningful protection to us.

Our commercial success also depends on not infringing on the patents and other proprietary rights of third parties. As our activities in the biotechnology and biopharmaceutical markets expand and as more patents are issued in the field, the risk that our technologies and products may give rise to claims of alleged infringement increases. Licensing or other arrangements for addressing these infringements or violations may not be available, or may not be available on commercially acceptable terms if we or our licensees are unable to obtain licenses from third parties for the use of their intellectual property in the manufacture of our products, we or our licensees may be unable to develop or market those of our products which are based in part on the intellectual property of others.

Product liability exposure

We may be exposed to product liability and other claims if third parties allege that our technologies or products have caused some harm.

If a third party sues us for an injury caused by our products or by products developed using our technologies, our liability could exceed our total assets. Because our vaccines that constitute our core products are administered to healthy

individuals, any adverse health consequences associated with such administration may be more apparent and perceived as less tolerable than similar side effects associated with the treatment of disease.

Lawsuits against us arising out of clinical trials may increase as more and more licensees utilize our technologies, thereby reducing our control over the manner of their use. We maintain product liability insurance in respect of all of our marketed products. We may seek to obtain additional product liability insurance in the future, though it cannot be assured that such additional insurance will not be prohibitively expensive, or that it will cover all of our potential liabilities. If we are unable to obtain sufficient insurance coverage at an acceptable cost or if we are otherwise unable to protect ourselves against potential product liability claims, we and/or our licensees may be prevented or inhibited from commercializing new products.

Product liability cases, claims and even relatively minor potential health risks associated with our products may give rise to adverse regulatory action, and/or a negative market perception of us and our products, resulting in a material adverse effect on our business, financial condition, results of operations and prospects. Though we believe we have strong defenses in these and other cases, including patent infringement cases, there can be no assurance as to the outcome of these matters and we could incur judgments or enter into settlements of claims that could have a material adverse effect on our results of operations.

Qualified personnel

We may not be able to continue to recruit and retain highly qualified management, scientific, manufacturing, sales and marketing and finance personnel. Competition for qualified personnel could be intense and may limit our ability to attract and retain qualified personnel on acceptable terms and may therefore significantly increase our labor costs. The inability to attract and retain highly skilled personnel on acceptable terms could have a material adverse effect on our business, financial condition, results of operations and prospects.

Hazardous biological materials

Our manufacturing, research and development processes involve the controlled use of hazardous biological materials. Certain of our laboratory

facilities are qualified up to Biosafety Level III (BSL-III), which allows us to work on-site with hazardous biological materials. Our operations may also produce hazardous biological waste. Given the inherently dangerous nature of certain biological materials we may work within our BSL-III laboratory facilities, we cannot eliminate the risk of accidental contamination or discharge or any injuries that result therefrom. Various laws and regulations govern the use, manufacture, storage, handling and disposal of these materials. We could be subject to civil damages and significant adverse publicity in the event of an improper or unauthorized release of, or exposure of individuals to, hazardous materials.

Competition laws

We cannot be certain that our licensing or other agreements are not in breach of applicable competition laws and will not be rendered void by the relevant competition authorities. In the past, we have not notified the European Commission competition authorities of any of our licensing or other agreements or sought clearance from any other competition authority. We take the view that these agreements are unlikely to be found to infringe European Union or other applicable competition regulations. It is possible, however, that current or future licensing or other agreements of ours could be found to infringe applicable competition regulations. If so, among other things, we may be subject to fines and claims of damages and these agreements may be considered void and unenforceable. Under the European Union's 2004 Technology Transfer Block Exemption Regulation, we may be required to review and possibly amend existing license and technology transfer agreements in the future. For example, if certain market share thresholds will be or have been reached in the relevant markets by those third parties that use our technologies to produce their products, the Regulation may require us to revise our agreements with those parties to ensure the agreements are in compliance with applicable European competition law.

Financial

Substantial use of capital

In the past, we have had to raise additional funds to acquire other companies and assets while continuing to research and develop our technologies and products. We also have incurred accumulated net operating losses since our incorporation.

Although the Company generated positive cash flow in 2008, we may have cash outflows and net operating losses in the future due to the occurrence of events that would consume our available capital resources. We may seek additional funding through public or private financing (including debt or equity financing), strategic alliances or other arrangements. We may not have access to additional financing and, if we do, it may not be on favorable terms. If we fail to raise sufficient funds, we may have to forego acquisitions, reduce our capital expenditures, scale back our product development, reduce our workforce and/or license products or technologies to others that we might otherwise commercialize ourselves.

Weakness in the global economy could negatively affect our business

The weakness of the global economy in 2008 was a challenge for many companies worldwide. The ongoing financial crisis became prominent in September 2008 with the failure or near-failure of several United States and European based financial institutions and the resulting deterioration in financial and market conditions spread around the globe. In recent months the financial crisis has adversely affected businesses in many industries and geographical areas all over the world at an unexpected pace.

The weakness of the global economy has not had a significant impact on our liquidity or on our ability to derive revenues from our operations. However, there can be no assurance that our liquidity will not be affected by recent and possible future changes in global financial markets and global economic conditions.

Financial distress and bankruptcies experienced by our customers and suppliers resulting from the recent global economic slowdown could impair their ability, as the case may be, to purchase our products, pay for products previously purchased or meet their obligations to us under supply agreements. This could lead to a material adverse effect in our revenues.

We do not know how long the current financial crisis will continue nor how severe it will ultimately be. In the long run, we may be affected if governmental agencies or supranational organizations decide to realign priorities and allocate fewer funds to public health initiatives. The financial crisis may have

a negative impact on the travel pattern, which is the key driver of our travel vaccines.

Foreign currency risk

The majority of our total revenues in 2008 were in currencies other than our functional currency, the Euro. Currency fluctuations may cause significant economic foreign currency exposure and transactional foreign currency exposure. Fluctuations in the currencies in which we do business relative to the Euro have affected our results in the past and, given the current economic climate and the substantial recent fluctuations in interest rates and currency exchange rates, may do so again in the future. Notwithstanding our efforts to foresee and mitigate the effects of changes in fiscal circumstances, we cannot predict with certainty changes in currency and interest rates, inflation or other factors affecting our business. Because of the variability of currency exposures and the potential volatility of currency exchange rates, we may suffer significant foreign currency losses in the future, particularly if the Euro strengthens relative to currencies in which a significant number of our operations are conducted. We engage on a limited basis in derivative transactions to hedge our foreign currency exposure. See section 3.2 'Foreign currency risk' in the financial statements for further details on our foreign currency risk.

Taxation

We are subject to the tax laws of the countries in which we operate as well as to European tax law. We may incur additional tax charges, including penalties, resulting from changes in tax laws or the interpretation of tax laws or from failure to comply with obligations required by relevant tax authorities. Disputes with tax authorities may arise with regard to the interpretation and application of tax laws. If any of these risks materializes, leading to tax costs associated with particular transactions being greater than anticipated, it could affect the profitability of our business as a whole. See note 5.4 'Income tax' in the financial statements for further details on our taxation.

Compliance and other

Ethical, legal and social issues related to the use of genetic technology

The use of genetic technology and materials derived from human fetal tissue, such as our PER.C6 technology, may raise ethical, legal and/or social

issues that could hinder regulatory approval, patentability or market acceptance of our technologies and the products developed using them. If these risks materialize they could have adverse consequences for our business since they could reduce or eliminate altogether potential markets for our own or our licensees' products.

Protective measures included in articles of association

Protective measures included in our articles of association, in accordance with Dutch law, may prevent corporate action and/or shareholder transactions that might be in the best interests of our Company or the shareholders. Among other things, our articles of association provide that our Supervisory Board may make binding nominations for the election of its members. Only a shareholders' resolution approved by an absolute majority of the votes cast, representing more than one-third of our total outstanding shares, can override those nominations. Furthermore, under Dutch law, we may issue preference shares to a foundation, Stichting Preferente Aandelen Crucell, or the Preferred Foundation, giving it preferred dividend rights, which may dilute the voting rights held by the holders of other classes of shares. The Preferred Foundation has an option to acquire a number of preference shares equal to the number of our total outstanding shares. The chairman of our Supervisory Board, Jan Oosterveld, and four independent members comprise the board of the Preferred Foundation. These and other provisions in our articles of association may have the effect of delaying, deterring or preventing corporate action that might be in the best interest of the Company or our shareholders and/or preventing our shareholders from selling their ordinary shares or ADSs at a premium to the market price. See 'Other information' and 'Articles of Association and Share Capital' for additional information regarding the preference shares and our articles of association.

US and other non-Dutch holders of our ordinary shares may not be able to exercise pre-emption rights.

In the event of an increase in our share capital, holders of our ordinary shares are generally entitled to certain pre-emption rights unless these rights are excluded by a resolution of the General Meeting of Shareholders or a meeting of the Management Board if so delegated by the General Meeting of Shareholders. However, US holders of our ordinary

shares may not be able to exercise pre-emption rights unless a registration statement under the Securities Act is declared effective with respect to the shares issuable upon exercise of such rights or an exemption from the registration requirements is available. No assurance can be given that any registration statement will be filed or, that if filed, it will be declared effective or that any exemption from registration would be available to enable the exercise of a US holder's pre-emption rights.

Shareholders may have difficulty protecting their interests as shareholders as we are a Dutch limited liability Company.

Dutch law and our articles of association govern issues regarding the legal organization, internal constitution, corporate authority and liability of members of our Management Board and Supervisory Board. Most of our offices and assets are located outside the US. In addition, a majority of the members of our Supervisory Board, all of the members of our Management Board and management team are residents of, and most of their assets are located in, jurisdictions outside the US. As a result, it may be difficult to serve process on these persons within the US. It may also be difficult to enforce a US court judgment against them in a US court or in a Dutch court or to enforce a Dutch court's judgment against them in a US court. This can include actions under the US securities laws. In addition, it may be difficult to enforce, in original actions brought in courts in jurisdictions located outside the US, claims under US securities laws. For a more complete discussion of potential difficulties in protecting your rights, see 'Articles of Association and Share Capital – Enforcement of Civil Liabilities'.

Share price volatility

Our ordinary shares and ADSs may have a highly volatile trading price. Shareholders may not be able to resell their ordinary shares or ADSs at or above the price they pay for them, the ADSs may vary in value and our share price may render us vulnerable to a takeover bid. Our ordinary shares are listed on NYSE Euronext Amsterdam and the SWX Swiss Exchange, and our ADSs are listed on the NASDAQ Global Select Market. The trading prices of ordinary shares of biotechnology companies in general have experienced significant volatility in the past and are likely to continue to be volatile. In addition, any negative change in the public's perception of the prospects of biotechnology companies could depress our ordinary share or ADS price regardless of our results of operations. Other broad market and industry factors, such as discussions on business combinations and a weak global economy may affect the trading price of our ordinary shares and ADSs, regardless of our performance.