Editorial

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Affordable vaccines for developing nations: fact or fiction?

» The productivity of the manufacturing processes has to increase: more output from a production system is needed, and the efficiency of the downstream process needs to be increased. «

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In the 19th and early 20th centuries, vaccines, together with significant improvements in quality of drinking water, resulted in a major reduction in mortality of the population. The effects cannot be underestimated, and by far exceed the effectiveness of other medicines such as antibiotics [1].

The first vaccine against variola virus causing smallpox was tested in 1796 in England by Edward Jenner. In Germany, Robert Koch discovered *Bacillus anthracis* in 1877, *Mycobacterium tuberculosis* in 1882 and *Vibrio cholera* in 1883. In 1885, Louis Pasteur developed a viral vaccine against rabies, and a vaccine against *Bacillus anthracis*. Based on Koch's discovery of the *M. tuberculosis*, Calmette and Guerin developed the BCG vaccine against tuberculosis, which was used as a vaccine for the first time in 1921. Although the BCG vaccine offers partial protection, it is still one of the most administered vaccines in the world.

In 1918–1919 the Spanish influenza killed an estimated 20–50 million people, and the onset of the Second World War triggered the development of a vaccine against influenza. An experimental vaccine grown in embryonated chicken eggs became available in 1937 and was introduced in the USA in 1945 [1]. The egg-based production platform is still used to produce vaccines against influenza, yellow fever, rabies and other viruses, which are administered to hundreds of millions of people worldwide each year.

Some viruses, such as polio, could not be grown in eggs. The cell culture processes to support research in virology were advanced significantly in the 1940s and 1950s. Salk and Sabin were able to produce large quantities of polio virus in cell cultures, leading to the development of an inactivated polio vaccine by Jonas Salk (1955) and an attenuated polio vaccine by Albert Sabin (1962).

The development of vaccines was supported by the governments in the west, resulting in the establishment of government-owned research facilities and private firms. In most developed countries, production systems were established from the 1950s to produce one or more of the six childhood vaccines (against tuberculosis, diphtheria, whooping cough, polio, tetanus and measles), among others, to safeguard a sufficient supply of efficacious vaccines.

The new vaccines increased revenue for the producers, but also increased the risks. Damages, even when it was not clear if the vaccine was the source, resulted in litigations in the USA in the 1970s. In addition, the costs for the R&D were increasing, as well as the costs to produce vaccines, partly due to introduction of more stringent GMP rules. Moreover, prices for vaccines were kept down by the buyers of the vaccines, mainly governments, resulting in eroding profit margins [101]. Of the more than 25 companies producing vaccines for the US market in the 1970s, only five are left [2].

The situation in Europe was different since the governments favored their national manufacturers, preventing a decrease in the number of manufacturers. However, in the 1980s and

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1990s the situation changed; globalization lowered the trade barriers. The result was an increase in mergers and acquisitions in the vaccine industry, as well as a drive to increase the scale of production and innovation. Large companies, such as Novartis, Sanofi Pasteur and GlaxoSmithKline were formed out of smaller private companies and government-owned facilities.

Although there is now a mature vaccine manufacturing industry in the west, each year an estimated 2.5 million people globally still die from vaccine-preventable diseases, for a large part in the developing countries. This is mainly due to a lack of full utilization of available vaccines resulting from low income, a lack of good medical infrastructure, and/or a lack of cold chain facilities. What is needed are innovations, such as high-yield technologies, to reduce the costs, improvements in adjuvants to increase efficacy and/or reduce the amount of antigen required, combination vaccines to reduce the number of vaccinations required, heat-stable formulations and improvements in packaging to reduce space for a vaccine in the cold chain [3]. Without innovation, the cost to develop, manufacture and distribute safe and efficacious vaccines, especially for the developing part of the world, is just too high to be commercially interesting for manufacturers in the west. Although all major pharmaceutical companies have charity programs for developing nations, a sustainable and healthy vaccine market cannot be built on charity.

Some companies in Brazil, Russia, India and China understood this and saw the opportunities for the developing world. Indian companies, such as the Serum Institute of India and Biological E, have built large facilities able to produce vaccines at affordable prices. This will also likely change as in India the salaries will increase, as well as the pressure on manufacturers to comply their production systems to international standards from regulators such as the WHO, the US FDA and the European Medicines Agency.

Therefore, to be able to supply affordable vaccines worldwide, the next step needs to be made. The productivity of the manufacturing processes has to increase: more output from a production system is needed, and the efficiency of the downstream process needs to be increased. To increase productivity, techniques that are able to support this are in development. An example of such a system is the iCellis™ bioreactor (ATMI, CT, USA), which is capable of growing adherent cells at high cell density while maintaining cell-specific virus productivity. The advantage of such systems is recognized by the veterinary vaccine industry: conventional labor-intensive production systems such as roller bottles can be replaced by the iCellis system, thereby decreasing the production costs.

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Another innovative system currently on the market to increase productivity is the alternating tangential flow (ATF) system. With the ATF system suspension cells can be grown in bioreactors to high cell densities, for example, >150 million cells per ml [4]. The ATF system is, therefore, an innovative system that can be used to increase product output per bioreactor, resulting in a lower cost price for the vaccine produced. This is now demonstrated for a polio vaccine in development, showing a 25- to 34-fold increase in the type 1 (Mahoney), type 2 (MEF-1) and type 3 (Saukett) strains when compared with the conventional process [5,6].

Intensified production processes result in relatively small-scale bioreactors of 500–1000 l in GMP manufacturing. This allows the use of flexible, disposable systems – thus reducing costs. Together with the introduction of precipitation technology and disposable unit operations, for example charged membranes in purifying viruses [3], the overall costs can be reduced significantly.

By introduction of such intensified production systems it will be possible to produce vaccines for the developing countries at an affordable price as requested by the WHO. The worldwide advantage of this intensification process is that vaccine supply is based on healthy economics and no longer based on the charity of companies or wealthy foundations.

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