Finally, measuring the level of implementation and the impact of vaccination policies on the epidemiological behavior of the disease or the pathogen is also a critical part of PMS for vaccines.

These processes are connected by a common thread, that is, regulation. Despite repeated promises of faster, simpler, more abbreviated regulatory requirements, the fact is that regulations have continued to increase in number and complexity at all stages of the vaccine development paradigm. Regulatory units are part of multidisciplinary pre-project assessments, as well playing an important role all along the development of the product, culminating in the licensing file; regulatory unit involvement continues post licensure after the vaccine is on the market. The new element that has emerged over the last decade has been an increased dialogue between industry and public regulatory bodies, which is making the overall process more predictable, albeit more complex and costly.

SOCIETAL ISSUES

In a world where the ''right to health care'' is becoming an increasing concern, this situation raises issues of access, which some companies have addressed for a long time already, as well as issues of perception of vaccines.

Access to Immunization

Intellectual Property

Intellectual property (IP) is key to the survival of companies and to the pursuit of innovation (2,10,31). It helps assure them an acceptable return on their research activities (which includes both successful and unsuccessful projects). This translates into pricing policies that will provide a financial return for a period of time. Sometimes this leads to a situation where certain new vaccines prove to be too expensive for developing countries unless external financial assistance is provided. This may be true in principle, albeit not necessarily in practice. All EPI vaccines except hepatitis B have lost their patent protection a long time ago, and these vaccines (including Hepatitis B) have been sold at very low prices to public buyers in less developed countries. Still, quite often supply is insufficient because of limited production capacity and the low prices, not because of patents. In other instances, demand does not materialize because of the lack of immunization services infrastructures or health policies in the developing countries.

The situation is obviously quite different for new patented products where the originating companies have to be guaranteed a fair return on their considerable investment. Maintaining or even reinforcing patent laws is a must in developed countries. This has taken place to some extent with the extension of patent laws in some countries, for new indications and for orphan products, where the very limited size of the potential market is a strong deterrent to industry's interest.

At the same time, patents have also been weakened in a number of ways: the early introduction of generics (through such mechanisms as ''Bolar'' in the United States), the large number of countries still not enforcing patent laws, and the threat of compulsory licensing not only in less developed countries but also sometimes in major markets (such was the case in the United States, linked to the bioterrorism scare). More generally, in the post-Seattle (antiglobalization movement), post-Pretoria (South African judicial ruling overriding patent), post-Doha circumstances, society at large has been applying strong pressures to make pharmaceuticals and vaccines more readily available to the poorest countries. Industry, while fully aware of these changes, needs to understand where this is taking such things as IP protection, which remains the main stimulus to innovation. Creative thinking is needed to develop new ideas to ensure compatibility between these apparently conflicting goals (46–48). It will probably take time and a mix of different steps from all parties to reach a satisfactory solution, even though substantial progress has already taken place.

As for generics, low-priced copies of vaccines could be seen as a way to level competition. But in practice, vaccines are very different from pharmaceuticals. A vaccine is licensed for manufacture in a given facility, and each batch has to be individually tested and released, whereas biologicals are not as strictly characterized as most pharmaceuticals. This makes it almost impossible for a true generic vaccine to exist, and the concept here is one more of ''biosimilars'' than of ''generics.''

Technology Transfers

One of the ways to improve access for the less developed countries has sometimes been envisioned via transfers of technology. While these transfers may look like an easy solution, heretofore in practice this has certainly not been the case. Setting up a manufacturing facility acceptable to regulatory authorities is not an easy task. It requires a significant financial investment, adequately trained people, a suitable local environment (especially regulatory for controls), and support from other partners. It also requires a large enough guaranteed market and several years to come on line (46). As a result, a technology transfer can only succeed if it is very well planned, through a stepwise approach and a learning process (32). An ill-planned/ill-conceived technology transfer will only result in failure, frustration, and resentment. Also, such transfers will have to be financially successful. Obviously, if prices are too low, this will prove detrimental for local companies, which need to invest heavily to catch up with their counterparts in developed countries.

With the emergence of viable, competitive local manufacturers in the major less developed countries such as India, Indonesia, Brazil, China, etc., the industrialized-country manufacturers have to decide whether to delocalize some productions or to enter in partnerships, joint ventures, or outright transfers of technology as an element of their long-term strategy (32). This has already taken place in a number of countries and will certainly develop further over the years.

Dual Track

Because of the vast needs and the strong downward pressures on vaccine prices for the poorest countries, practical solutions have had to be identified to ensure supply. Over time, this has developed into a situation where, for many vaccines, a ''dual track'' often exists between industrialized versus developing countries, for example, acellular pertussis versus whole-cell pertussis vaccines, Jeryl Lynn–based measles/mumps/rubella (MMR) versus monovalent measles, IPV versus OPV, combined versus monovalent vaccines, monodose versus multidose vaccines, thiomersal-free versus thiomersal-containing vaccines, and wide access versus limited access to new vaccines.

Obviously, dual track has been closely related to dual pricing. Although ethically arguable, in principle, such a situation has proved to be a pragmatic answer to a difficult, complex situation. Taking a purely ideological stance can be counterproductive. What is probably a better answer is to make sure