COMMENTARY

Regulation of vaccines: strengthening the science base by Julie Milstien

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THE author, Dr. Julie B. Milstien, is a well-known expert in everything related to vaccines and biologicals. Her knowledge, experience, and expertise are based on hard work and dedication of her entire life to these subjects. She knows existing vaccine quality control systems worldwide. She has worked at the USFDA, at the Pan American Health Organization (WHO's Regional Office for Americas) and more recently at the World Health Organization in Geneva, leading vaccine quality programs. She has participated directly or indirectly in all activities related to quality, development, and production of vaccines: overseeing development of documents (guidelines, minimum requirements, scientific papers, project and program reports), meetings, training, inspection, and many other related activities. And in each activity, she was actively engaged. Thus her recognition worldwide is very well deserved. She recently retired from WHO.

This paper comes at a very good time. In the last years, new technologies have been applied aggressively to the development of new vaccines. Worldwide, dozens of vaccine development meetings take place, where new discoveries and new research approaches are presented at a pace never before seen. The Jordan Report for 2002 (1) demonstrates the rapid growth of knowledge and information about new vaccines. And in that context, Dr. Milstien's paper alerts us to another concern emerging along side vaccine innovation: the regulatory technologies and strategies, which must keep pace with accelerated expansion of vaccine development.

People everywhere perceive the importance of vaccines and immunizations for humanity. Almost thirty years ago smallpox was eradicated globally; the global eradication of poliomyelitis is set for 2005;

and reported vaccine preventable diseases have declined to an all-time low. Vaccines are truly one of the most important tools of public health (2).

After a monumental accomplishment such as the eradication of smallpox and then poliomyelitis in the Americas, our memories of the fear and tragedies caused by these viral diseases are easily forgotten; the perceived value of vaccines that protect the population wanes rapidly. How can we maintain vividly and continuously in the mind of the authorities, policy makers, and the general population, the need to support vaccination?

How can new vaccines that are more advanced technologically, cause fewer reactions, and are more immunogenic, be brought more rapidly into general use, including in developing countries? How can governments expedite regulatory harmonization in order to reduce costs and facilitate the global use of new vaccines? Lievonen estimated that harmonization could reduce vaccine development costs by 20 per cent and reduce by six months the time for registration (3).

One essential step in the process of vaccine introduction is becoming more complex and expensive—meeting regulatory requirements in both industrial countries and developing countries.

For many years, the US FDA has exerted leadership in every aspect of vaccine regulation: norms, requirements and specifications, and quality control methods that many other countries have adopted. In recent years, two additional entities now play important roles globally. The European Union has strengthened its Regulation and Quality Control System to achieve harmonization of norms, requirements, and regulations and the WHO has also pushed actively for quality control systems by organizing technical meetings, quality control laboratories, and training networks, while offering biological standardization and providing reference materials. WHO created and publicized its Minimum Requirements for vaccines, one of most important publications for regulators and manufacturers in developing countries.

The public understands the importance of a quality control system to guarantee quality. In some developing countries in the Americas, where the National Regulatory Authority (NRA) lacks an ability to perform "release quality control" testing, visual quality control is still performed. Yet this relatively simple examination has detected some important imperfections in vaccines from well known international vaccine manufacturers. In other countries where vaccine production

is actively pursued, they follow WHO's recommendations and are strengthening their NRAs and the National Quality Control Laboratories (NQCL).

This is the case in Brazil. The Brazilian NRA—the Agency for Sanitary Surveillance (Agencia Nacional de Vigilância Sanitária—Anvisa)—was established in 1998 as an autonomous executive agency linked to the Ministry of Health. The National Congress approves the appointment of the president and directors and they have a mandate to strengthen regulations, norms and requirements, which are already comparable to developed countries. The Brazilian National Immunization Program (NIP) has gained the confidence of the population by using vaccines of high and guaranteed quality. All the vaccines used in NIP must be tested and released by the National Quality Control Laboratory, thus avoiding poor quality vaccines.

Vaccine regulation is aided by modern communication systems. They make it possible to transfer information from one country to another in real time. The Internet means that no matter where something is published or discussed, the same information is available anywhere that someone searches for it. When, for example, the FDA decided to discontinue use of Rotavirus vaccine in the US, due to high incidence of intussusceptions in vaccinated children, this information reached not only the health authorities, who could carefully assess the information, but also reached the general population. The results were problematic, for thereafter, it became difficult or even impossible to convince authorities to use the vaccine, even if, despite intussusceptions, the vaccine could be shown to be highly cost effective.

Dr. Milstien tells us that in the past, FDA regulation was usually strengthened only after a major disaster occurred. Public authorities acted only after disasters to identify the causes of the problem, to look for new and improved quality control methodologies, and to revise regulation and norms. Obviously, they wanted to avoid a repeat of the particular problem and make the vaccine safer for use in general population.

In Brazil, we also experienced severe adverse reactions caused by poor vaccine quality.

– Several lots of yellow fever vaccines formulated with human serum infected hundreds of vaccine recipients and caused several deaths (4);

– Rabies vaccine produced in 1962 using the Semple method (rabbit neural tissue), killed 18 of 60 vaccine recipients in Fortaleza, Ceará, because of the presence of active virus in the vaccine (5);
– Rabies vaccine produced using the Fuenzalida and Palacios method(6) (cerebral tissue of newborn mice) was widely used in South and Central America where it caused neurological side reactions; from 1975 to 1978 Brazil registered 17 severe neurological reactions, with 11 deaths (7).
– In the early 1970s the measles vaccine used in the NPI lacked adequate potency;
– We also saw bacterial contamination of multi-dose vaccine vials after drawing up vaccine five to six times with a needle puncture.

Even in developing countries where vaccine preventable disease still occur, there is growing concern about adverse reactions to vaccine. Mothers are beginning to worry about hypotonic hyporesponsive syndrome seen after whole cell DTP vaccinations. The rare vaccine-caused paralysis associated with Oral Poliomyelitis Vaccine (OPV) is no longer acceptable since the eradication the disease. In 1995 Chen (8) noted that whenever control and/or elimination of a vaccine preventable disease is achieved, the adverse reactions caused by vaccines gain new attention. As perceptions change, the population demands vaccines which do not cause adverse reactions and by implication more stringent and complex regulations and requirements for licensed vaccines.

Dr. Milstien reminds us that outdated animal tests are still required, offering us colorful examples. Another example that corroborates her observation is monkey neurovirulence testing for Yellow Fever vaccine—a test still considered essential for vaccine approval. Ten rhesus monkeys must be inoculated intracerebrally with new working seed (one additional passage) and compared with 10 additional monkeys inoculated with a reference 17D virus. The monkeys are observed clinically and after 30 days they are sacrificed. The histopathology of the central neural tissue and internal organs are then observed and compared. But no relationship has been demonstrated between the number of lesions seen in monkeys with different viral strains and clinical events in humans. This phenomenon has been poorly studied and it may not be possible to do such a study (9).

To detect less frequent side effects, we may need to conduct larger phase 3 clinical trials of vaccines. But in addition to the high cost of large trials, it is increasingly more difficult to organize them because of the general population's perception of being used for "testing." Benefits are not tangible. We believe that to generate more confidence in the general population, government health systems must actively participate in organizing trials and provide adequate information to the population.

Dr. Milstien's proposal for future directions would provide some important alternatives for regulators and manufacturers.

- Risk-benefit analysis can include developing countries when estimating global benefit. Infectious agents, vectors (insects and birds), and healthy carriers do not know national boundaries. Thus vaccine trials for new vaccine should be organized in many sites to account for epidemiological differences in incidence, strains, and impact of the disease. For example, the Rhesus rotavirus vaccine, mentioned above, was withdrawn in the United States because of intussusceptions after rotavirus vaccination. Although this decision may have been appropriate for the United States, this vaccine could play an important role in Latin America and elsewhere, where the severe disease caused by rotavirus infection has high prevalence.
- The adoption of state-of-the art- pharmaceutical science is a must. Incredible advances in science, led by molecular biology, makes it possible to map the DNA/RNA sequence infectious pathogens. This knowledge can be applied to develop new products, but it should be also applied quality control methods from the very start of vaccine development. All vaccine development projects should use new molecular technologies to create quality control methods. Nucleic Acid Testing (NAT) is already employed to assess certain viral vaccines such as Mycoplasma. It is now possible to use RNA sequence analysis to compare a virus isolated from a case of Yellow Fever that may be associated with vaccine and a control 17D virus (10)
- The kind of quality control system that is used in pharmaceutical production and regulation can now be extended to vaccine, including accreditation of control laboratories. Moving to a system that relies on chemical identity deserves to be discussed by all participants to assure a firm and credible system.

International collaboration is also a must, in order to achieve harmonization of procedures, methodologies, specifications and to have comparable data and results. The WHO global training program should be supported and strengthened and harmonization should be the global target.

As we have noted before, governments of some developing countries where local production of vaccines exists are making important investments to strengthen their NRAs and NQCLs. Although, our professionals are highly educated and many hold PhDs, there are very few with experience in production, quality control, and in the field studies. In order for us to respond to the challenge put forth by Dr. Milstien—to redefine the approaches and parameters of regulation, regulators too, must be trained in "know-how" and "know-why" of vaccine production and be well informed about their country's epidemiological situation.

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