Cooperation between regulatory authorities from developing countries in the evaluation of vaccine clinical trials

Cooperação entre agências reguladoras de países em desenvolvimento para avaliação de ensaios clínicos de vacinas

Sérgio de Andrade Nishioka [1]

[1] *Núcleo de Gestão do Sistema Nacional de Notificação e Investigação em Vigilância Sanitária, Agência Nacional de Vigilância Sanitária, Brasília, Brasil.*

Correspondence
S. A. Nishioka
Núcleo de Gestão do Sistema Nacional de Notificação e Investigação em Vigilância Sanitária, Agência Nacional de Vigilância Sanitária.
Anvisa Unidade 2/SEPN Q. 511, Bloco A, Ed. Bittar II, 2º andar, Brasília, DF 70750-541, Brasil.
sergio.de.andrade.nishioka@gmail.com

Many believe that it is convenient and safe for developing country national regulatory authorities (NRAs) to license or register new vaccines, based on previous assessments made by a developed country regulatory agency. According to this "pragmatic" approach, the world is divided into those who know how to do an assessment of the quality, efficacy and safety of a new vaccine, and those who do not, and it is implied that it is simply not worthwhile for the latter to try to repeat what the former has already done, because it would be expensive, time consuming, and would possibly not be feasible for them. In other words, it would be an inefficient duplication of efforts. By the same token, developing country NRAs should not waste time assessing the scientific merit of clinical trial protocols, and should limit themselves to evaluating such protocols from an ethical perspective.

As a counter argument, it can be claimed that the world has now entered a new era whereby new vaccines are being developed that target diseases which only occur or are more prevalent in developing countries. Thus, clinical trials of these vaccines are being or will be conducted in developing countries, and some of these products will be first licensed/registered in the same countries. Moreover, licenses of "old" vaccines that are still used in the developing world will not be renewed by some NRAs from developed countries, as is the case for the European Medicines Agency (EMEA), for example. Finally, manufacturers from some developing countries have acquired technologies transferred from developed country counterparts, and are developing new products such as vaccine combinations that have to be assessed by clinical trials before being submitted for licensure/registration.

Therefore, at least the more advanced NRAs from developing countries now need to know how to analyze (phase I, II and III) clinical trial protocols, follow up at least the clinical trials conducted in their territories through good clinical practice (GCP) inspections and adverse event reporting, assess data from these clinical trials as evidence for licensure/registration, and do post marketing surveillance of these products.

Brazil, represented by the Agência Nacional de Vigilância Sanitária (National Health Surveillance Agency – ANVISA), the Brazilian drug regulatory agency, has, in recent years, been involved in World Health Organization (WHO) and Pan American Health Organization (PAHO) initiatives aimed at improving international cooperation between NRAs in the field of vaccines. There follows a brief summary of this involvement and some personal reflections.

In September 2004, the Developing Countries' Vaccine Regulators Network (DCVRN), an initiative from WHO, was launched after over two years of preparation [1,2]. The original idea was for the establishment of an NRA network of developing countries aimed at promoting the strengthening of the procedures for evaluating clinical trial proposals and clinical data. Nine countries (Brazil, China, Cuba, India, Indonesia, Korea, Russia, South Africa and Thailand) fulfilled the eligibility criteria of having WHO pre-qualified vaccine manufacturers, of being fully functional NRAs (i.e. meeting six critical regulatory functions or having a government endorsed workplan with timelines to achieve this), of having domestic expertise in research on new vaccines and recognized medical institutions for clinical research on the control of infectious diseases, and of being likely to be the first to trial and license/register new vaccines. Representatives from these countries have met six times since then, and other than organizing the network structure and regulations, have participated several scientific sessions for discussing a series of vaccines (e.g. rotavirus, tuberculosis, HIV, HPV, Japanese encephalitis), in some occasions with the joint participation of representatives from more developed (FDA) and less developed agencies.

From 2003 PAHO has organized a series of regional meetings involving countries from Latin America in order to make an inventory and better understand the clinical trial evaluation processes in different countries from that region, to develop capacity building activities, and to discuss a novel rotavirus vaccine that was to be introduced in the region for the first time worldwide. In 2005 a working group

on vaccines was created within the Pan American Drug Harmonization (PANDRH) initiative, which is not restricted to countries from Latin America and the Caribbean, but also counts on the participation of the United States and Canada [3].

As result of these collaborations it can be said that the members and other participants of these initiatives have realized: (a) their different strengths and weaknesses; (b) that they can benefit from sharing and exchanging information (e.g. standard operating procedures (SOPs) for the assessment of clinical trial applications, procedures adopted for GCP inspections); (c) that the assessment of novel/new vaccine dossiers does not necessarily have to be the same as those performed by agencies from more developed countries, as different questions may be raised that may need additional evidence to be answered. A good example of the latter was the issue of possible interaction between two new rotavirus vaccines with (concurrent or not) oral polio vaccine (OPV), that is relevant to countries where such vaccines are used instead of inactivated polio vaccine (IPV), most commonly used in developed countries. Other issues that are relevant to oral rotavirus vaccines and considered by developing countries to be important were the roles of breastfeeding, malnutrition, immunodeficiency and vaccine viral shedding.

Having represented ANVISA in both initiatives up to 2006 I would like to share my views that: (1) collaboration between NRAs in the evaluation of vaccine clinical trials and perhaps also marketing applications is necessary in this changing era; (2) both WHO and PAHO initiatives have shown that collaboration has strengthened the capacity of developing country NRAs to deal with clinical trials of new vaccines; (3) the developing country perspective may impact (either accelerate or delay) the availability of a new vaccine in the market; in the rotavirus vaccine cases it delayed registration in many countries because requirements that were additional to those asked by more advanced regulatory agencies were requested by developing country NRAs; (4) delays in access to these new vaccines is not a disadvantage if these requirements are relevant to their efficacy and safety in developing country settings; (5) increasing standards of assessment from developing country NRAs should make developing country manufacturers keep up with internationally accepted standards, which should lead to better quality locally produced vaccines; (6) multinational manufacturers' plans for new vaccine developments should take into account developing countries' perspectives.

1. World Health Organization. Report on the meeting on national regulatory authority (NRA) networking for new regulatory pathways. Geneva: World Health Organization; 2003.
2. World Health Organization. Developing countries' vaccine regulators network establishment. http://www.who.int/immunization_standards/vaccine_regulation/dcvrn/en/ (accessed on 22/Nov/2007).
3. Red Panamericana para la Armonización de la Reglamentación Farmacéutica, Organización Panamericana de la Salud. Grupo de trabajo en vacunas. http://www.paho.org/spanish/ad/ths/ev/GTVacunas.htm (accessed on 22/Nov/2007).

Submitted on 28/Nov/2007
Approved on 19/May/2008