Research Update

CLINICAL INVESTIGATION

Helping each other regulate clinical trials: a network of vaccine regulators from developing countries

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In the early 2000s the WHO acknowledged the growing importance of national regulatory authorities from emerging countries to face the challenge of new production technologies and the emergence of vaccine manufacturers from these same regions. The establishment of the Developing Country Vaccine Regulators' Network (DCVRN) was part of the WHO's strategy of strengthening national regulatory authorities in vaccine-producing countries and promoting their collaboration through networking. The interaction among the DCVRN members during the network's 8 years of existence has facilitated the development of these regulatory authorities in areas such as good clinical practice inspections and reporting of adverse events during clinical trials, and the proposal of an investigational new drug-like system for developing countries. The DCVRN has interacted, among others, with regulators and with vaccine manufacturers, and has had technical/scientific discussions on most novel candidate vaccines of interest to developing countries and also on old vaccines produced by new manufacturers. Recent administrative changes at the WHO, which have put vaccines and medicines under the same umbrella, offer challenges but also opportunities for the future of the DCVRN.

Keywords: clinical trial • developing country • network • regulation • vaccine

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The Developing Country Vaccine Regulators' Network (DCVRN), established in 2004 by the WHO, comprises representatives from vaccine regulatory authorities from nine emerging countries. Its purpose is to contribute to the strengthening of the National Regulatory Authorities (NRAs) of developing countries where vaccines are manufactured, particularly in the area of authorization of clinical trials and evaluation of clinical data. In this article we will present a brief account of the conceptualization of a network of developing country vaccine regulators, the creation of the DCVRN, its achievements and limitations, and the opportunities and challenges that it faces now and will face in the future.

The need for a network of vaccine regulators

The development of new production technologies and the emergence of vaccine manufacturers in developing countries led to the WHO's acknowledgement, in the early 2000s, of the challenge represented by new vaccines in terms of quality assurance [1]. In order to address this issue, the WHO proposed a definition of 'vaccines of assured quality', which depended on the existence of a competent and functional regulatory authority, as assessed by an external expert team using widely agreed indicators, to regulate the product [2]. Strengthening NRAs and networking among regulatory authorities were identified as useful approaches to be applied both at the national and the international levels to improve vaccine quality and

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its perception [2]. The quality of clinical trial regulatory oversight could be improved by strengthening the capacity of NRAs in this area; and networking among regulators could be a good strategy to accelerate the process of developing systems and harmonized criteria for clinical trial regulation.

In November 2002 a 2-day 'Meeting on NRA networking for new regulatory pathways' was held at the WHO headquarters in Geneva (Switzerland) [3]. Nine countries were invited for this first meeting – Brazil, China, Cuba, India, Indonesia, Republic of Korea, Russian Federation, South Africa and Thailand – each a vaccine manufacturing country with significant educational, research and industrial capabilities and experience with clinical trials. These countries were identified by the WHO as the ones with the "*potential to create a network to accelerate production and clinical testing of new vaccines in developing countries where they are needed*" [3]. The outcomes of this meeting included an action plan for establishing a network of developing country vaccine regulators to address the challenges of regulating development of new and emerging vaccines, with a focus of clinical trials but recognizing that the activities might be broader than that.

The DCVRN was established in September 2004 in a meeting in Bangkok, Thailand. The nine countries represented in the 2002 meeting in Geneva became network members by fulfilling the criteria of having at least one manufacturer with a prequalified vaccine for supply through UN agencies, for use in national immunization programs and its NRA fulfilling the six critical regulatory functions required by the WHO, or having a government-endorsed work plan to achieve this. Membership criteria were clearly linked to the WHO vaccine prequalification, a service provided by the WHO for UN purchasing agencies, which provides independent opinion/advice on the quality, safety and efficacy of vaccines for purchase, ensures that candidate vaccines are suitable for the target population and meet the needs of the program, and ensures continuing compliance with specifications and established standards of quality [101]. The six regulatory functions mentioned are: published set of requirements for licensing; surveillance of vaccine field performance; system of lot release; use of laboratory when needed; regulatory inspections; and evaluation of clinical performance [102].

8 years of DCVRN: achievements & limitations

The DCVRN mission is to support and promote the strengthening of the regulatory oversight during the clinical development of vaccines, authorization and inspection of clinical trials, evaluation of investigational products, evaluation of registration dossiers and postmarketing surveillance in developing countries. The DCVRN has agreed terms of reference **(Box 1)** and member representatives meet regularly to further the defined objectives.

DCVRN membership has evolved over time, and there are currently nine members **(Box 2)**. Over its 8 years of existence the DCVRN members have met once or twice a year to discuss regulatory issues. There were 13 meetings during this period of time, hosted by the member countries or by the WHO, in Geneva.

The subjects discussed in these meetings can be categorized as: network organization, interactions with other organizations, learning from each other, and technical and scientific sessions related to vaccine development **(Box 3)**.

The DCVRN benefits very much from its interaction with regulators from agencies considered to be at more developed stage, such as the US FDA, the European Medicines Agency, Health Canada and Australia's Therapeutic Goods Administration, but the expectations for the participation of guest regulators from these bodies in the meetings is to exchange information, not to impose models. On the other hand, other regulators at a lesser stage of development benefit from their participation as guests in DCVRN meetings. As examples of these, there are neighboring countries of the member country where a DCVRN meeting is held, and representatives of the African Vaccine Regulatory Forum – a WHO-supported network of vaccine regulators from sub-Saharan Africa. The DCVRN and/or its members also interact with manufacturers (e.g., the Developing Countries Vaccine Manufacturers Network), ethics committees and national immunization technical advisory groups [4]. The interactions with manufacturers of novel vaccines, who are invited to special sessions of meetings of the network, have been considered of particular interest by DCVRN members.

Perhaps the most useful benefit of the DCVRN for its members is to exchange experiences and to work together in order to achieve a common goal. A concrete example of the former is the monitoring of clinical trials through Good Clinical Practice (GCP) inspections. When the network started, in 2004, GCP inspections were not routinely conducted in several member countries and the procedures were not standardized. The experience of sharing regulations and the joint development of standard operating procedures has facilitated the introduction of standardized GCP inspections by regulators in member countries. The development of a (nonpublished) document on an investigational new drug-like system for developing countries is an example of a positive outcome following discussion of a subject of common interest to all the members, when few had such a system incorporated in their regulations. This system has been useful in assisting regulators of member countries to deal with the clinical development plan of novel vaccines.

Box 1. Developing Country Vaccine Regulators' Network terms of reference.

- Encourage and facilitate information exchange among the NRAs regarding national legislation and regulations, and through the joint development of guidelines and policies relating to the regulatory control of domestic or imported vaccines, in particular regulatory oversight of clinical trials (clinical trial authorization and inspections) and clinical data evaluation
- Develop guidelines or procedures relevant to the regulatory oversight during clinical development of vaccines, authorization and inspection of clinical trials or evaluation of registration dossiers
- Discuss NRA policies aimed at advancing mutual understanding of their respective levels of expertise and identify the potential for collaboration and joint regulatory activities
- Identify internationally recognized standards consistent with WHO guidelines for clinical evaluation of vaccines. If guidelines are not available, the DCVRN may propose ideas for consideration of WHO-relevant expert or advisory groups and collaborate in the development of such guidelines
- Enhance the expertise and effectiveness of the NRAs in vaccine evaluation during clinical development, including clinical aspects and investigational product evaluation, and suitability of clinical data for registration (evidence of safety and efficacy for the target population)
- Promote information exchange through: encouraging enrolment of network participants in training courses on clinical evaluation developed by the WHO; inviting relevant clinical and regulatory experts to present at DCVRN meetings, as appropriate; coordinating joint activities; providing expert assistance for regulatory evaluation, upon request; and any other relevant activities as agreed by DCVRN members and the WHO

DCVRN: Developing Country Vaccine Regulators' Network; NRA: National regulatory authorities.

Requirements for the conduct of clinical trials for some candidate novel vaccines and the requirements for their licensure have been discussed in DCVRN meetings, and these vaccines are revisited from time to time as new information becomes available. New tuberculosis vaccines, for instance, were discussed in three different meetings, starting from a general discussion [5] and subsequently going to more specific discussions on questions considered key for the candidate vaccine developers, regarding the conduct of clinical trials (e.g., acceptability of the use of a new candidate tuberculosis vaccine compared with BCG in newborns), and requirements for licensure in different countries. Different aspects of the regulatory pathways for clinical investigation and licensure of dengue vaccines have been discussed on three different occasions [6].

An independent expert assessment of the activities of the DCVRN, commissioned by the WHO in 2009, concluded that the evidence available indicated that the DCVRN had had a significant and positive impact and that the individuals who had participated in the meetings, as well as the NRAs they represented had benefitted from DCVRN activities [Unpublished data]. There is a single published paper (letter to the editor) in which a regulator expressed his opinion of the benefits of the cooperation of regulatory authorities from developing countries in the evaluation of clinical trials [7]. In that letter, the author justifies the need for the strengthening of regulatory capacity of developing country regulators from a regulator's perspective, which overlaps in part with, but is not identical to, the WHO's. The need for self-sufficiency in terms of regulatory capacity is justified in part by the role of these regulators to oversee the development and decide on the licensure of vaccines produced by local manufacturers. The benefit of the collaboration between different agencies from developing countries was highlighted by the example of oral rotavirus vaccines and their potential interaction with oral polio vaccines. This is an issue of extreme interest for developing countries, where oral polio vaccines was the choice for immunization against poliomyelitis, and of lesser importance to regulators of some developed countries where inactivated polio vaccines were used instead.

DCVRN representatives are employees of their NRA with a full portfolio of functions and responsibilities and this has limited their ability to actively participate in DCVRN activities outside the time around the network meetings. In the initial years after the establishment of the DCVRN, the WHO was able to support two meetings per year, but over time the countries themselves have taken part of the financial responsibilities to sustain the

Box 2. Developing Country Vaccine Regulators' Network current members (as of November 2012).

Representatives from the National Regulatory Authorities of:

- Brazil
- China
- Cuba
- India
- Indonesia
- Iran
- Republic of Korea
- South Africa
- Thailand

Box 3. Subjects discussed in Developing Country Vaccine Regulators' Network meetings[†].

Regular review of the Network organization and functioning

Interactions with:
- Other regulators
- Manufacturers and interest groups
- Ethics committees
- National immunization technical advisory groups

Learning from each other:
- Good clinical practice inspections
- Reporting adverse events during clinical trials
- Investigational new drug-like system for developing countries

Technical/scientific:
- Novel candidate vaccines; for example, dengue, HIV, human papillomavirus, Japanese encephalitis, malaria, rotavirus, tuberculosis and typhoid
- Old vaccines produced by new manufacturers have also been tabled; for example, diphtheria–tetanus–pertussis-based combination vaccines
- New adjuvants

[†]For several of these topics the Developing Country Vaccine Regulators' Network has produced 'Points to Consider' documents for members and for the WHO Expert Committee on Biological Standardization.

network and the organization of more than one meeting per year became less feasible. Since 2011, a web-based meeting has been organized to supplement the face-to-face meetings. However, this has some limitations such as shorter duration (1.5-h sessions) and the time differences between countries requires duplication of the same discussion, coordinated from the WHO headquarters in Geneva once for Asian countries and once for American countries, while participants from Europe and Africa have the choice to join one or the other.

Future perspective

The reasons for the establishment of the DCVRN remain relevant. As a WHO initiative that started from the Immunization, Vaccines and Biologicals department, it has focused on vaccines and vaccine development. Licensure of vaccines (plus other biologicals) and registration of medicines are usually performed by different units in the regulatory agencies that are part of DCVRN, whereas authorization of clinical trials with vaccines and other products may be performed within the same unit. Focus on vaccines has strengthened the regulatory agencies but it can be argued that it creates an artificial separation among products in respect to authorization and monitoring of clinical trials, including GCP inspections and adverse events monitoring. Notwithstanding that, several members have noted that the DCVRN activities have had an overall beneficial effect on the functions of their NRA.

Current restructuring within the WHO, as of November 2012, has brought vaccines and medicines prequalification and NRA strengthening groups under the same umbrella. It may be expected that in the future the DCVRN will benefit from the synergies between them. It is important both for the WHO and for the regulators who are DCVRN members to take advantage of the lessons learned from the 8-year experience of the network. Although the benefits of participating in the DCVRN cannot be quantified or claimed to be exclusively due to the network, the collaboration between regulators should be continuously encouraged and facilitated by the WHO.

Executive summary

- The WHO supported the establishment of the Developing Country Vaccine Regulators' Network (DCVRN) to address the challenges of new production technologies and of new national vaccine manufacturers in order to ensure the availability of vaccines of assured quality.
- This network of nine regulators has developed collaborative work to improve their ability to authorize and monitor vaccine clinical trials and to evaluate clinical data.
- DCVRN meetings have allowed the interaction of their members with other regulators, manufacturers and sponsors involved with vaccine development and clinical trials, and the discussion of several novel vaccine candidates.
- Collaboration between regulatory authorities through networks such as the DCVRN is a useful strategy to strengthen their capacity and should be encouraged and supported.

Disclaimer

The opinions expressed in this article are those of the authors and do not necessarily represent the official position of the WHO, the Centro para el Control Estatal de Medicamentos, Equipos y Dispositivos Médicos or the Developing Country Vaccine Regulators' Network.

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