

**Report of the Regulatory Forum on
Update on Clinical Experience with Rotavirus Vaccines**

Held during the

**Sixth Meeting of the
Developing Countries Vaccine Regulator's Network (DCVRN)
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Summary

Members of the Developing Country Vaccine Regulators Network met in closed session with US FDA and EMEA regulatory experts to review the progress made in evaluation of clinical evidence used as the basis of registration in member countries, and the progress made towards registration and introduction of these vaccines. There were also meetings with the manufacturers of the two vaccines currently being introduced world-wide. The experience and continued concerns of the regulatory authorities in the USA and EU were described.

The DCVRN has noted some issues that should be considered in relation to the registration and introduction of rotavirus vaccines.

Background

The DCVRN held a rotavirus vaccine Scientific Session during the 3rd meeting in Bangkok 2005.

At that time very few countries had licensed rotavirus vaccines for distribution, and several large studies were in progress. The extent of the disease and disease burden was described.

The science of the vaccines' development had been presented, and the design and rationale for the clinical trials described. The results of the studies with developmental vaccines was presented.

The experience with RotaShield, a rhesus-human reassortant vaccine in the USA was described and the issue of increased incidence of intussusception [IS] in vaccinees was highlighted. The extra surveillance and additional trial participants that had been enrolled in attempt to prove or disprove a link between the vaccine and IS was described.

At the time of this 6th DCVRN meeting, Rotarix is registered in the EU, Latin America and in many other countries in the world, while RotaTeq is registered in the USA and the EU and is undergoing regulatory review in many other countries.

The Experience of the DCVRN member countries in the regulatory review, conduct of clinical trials and registration of these vaccines was discussed by the members. The post registration commitments required by the various regulatory authorities was described. The experience in use of the vaccine was also reviewed.

Rotarix manufactured by GSK in Belgium, is a live, attenuated G1(P8) human rotavirus oral, vaccine; Freeze-dried for reconstitution in a specific buffer solution. Two doses from 6- 12 weeks of age, with 4-10 week dosing intervals is recommended. Protection against any severe rotaviral gastroenteritis is claimed

to be >90%, and significant protection from any form of rotaviral gastroenteritis has been shown in clinical studies.

RotaTeq, manufactured by Merck & Co in the USA, is a live, bovine-human reassortant, pentavalent (G1, G2, G3, G4 & P8) oral rotaviral vaccine. It is a liquid formulation. Three doses from 6-12 weeks of age with 4 - 10 week dosing intervals are recommended. No dose should be given after 32 weeks of age. Protection against ~~any~~ severe rotaviral gastroenteritis has been shown to be 98% and protection from any grade of severity of rotaviral gastroenteritis has been shown to be 74% in clinical studies.

In the phase 3 Rotavirus Efficacy and Safety Trial (REST), no increased risk for intussusception was demonstrated for RotaTeq within 42 days of any dose.

DCVRN Considerations and actions

- 1 There is concern about the significance or validity of small Phase IIIb clinical trials that have been conducted in some developing countries with regard to scientific ability to define safety and efficacy. These concerns relate to the small numbers of participants and the anticipated immunogenicity end points. At this time, there is no immunologic correlate of protection against rotavirus disease.
 - 1.1 The DCVRN will explore with these member countries, the concerns of that led to the conduct of these studies.
 - 1.2 The DCVRN proposes that guidelines be developed to define useful Clinical Trials that will meet the concerns of the Developing Country Regulatory Authorities.
- 2: New and novel rotavirus vaccines are known to be under development, including by developing country manufacturers. The scale and design of clinical studies that will be needed to ensure safety and efficacy of these new and novel rotavirus vaccines need consideration.
- 3: The current knowledge does not support the interchangeability of the two Rotavirus vaccines. The WHO and DCVRN regulatory authorities should be alerted to this concern and suitable science-based advice provided to countries where both vaccines may be distributed.

Summarized Presentations

DCVRN Member Reports:

Brazil: José Evoide

Since introduction of Rotarix, 27 cases of IS have been detected, occurring within 30 days of vaccination. Since over 4 million doses have been distributed this remains a small number but may indicate an increased relative risk.

Korea: SY Kang

No rotavirus vaccine is registered in Korea. Two small Phase IIIb studies, one with each vaccine, have been conducted in Korea. There were no unexpected results, but the numbers were too small to detect a signal.

South Africa; JA Southern

Rotarix has been registered in SA and about 50 000 doses distributed. Reported AEFIs include 1 x mal-administration and 1 x IS. The rationale for registration and the post-registration commitments of GSK were explained. RotaTeq is in the regulatory review process.

India: AB Ramteke

No rotavirus vaccine is registered in India. Two Phase IIIb trials have been conducted - as in Korea. Three locally manufactured rotavirus vaccines are under development. No trials to date.

Indonesia: Antonia Tyas Retno Utami

Rotarix and RotaTeq vaccines are in the regulatory review process. There is development of a local Rotavirus vaccine - no trials with these to date.

Thailand Y. Lawaranpraset

Rotarix was registered in 2005 and introduced at designated hospital immunization centres. RotaTeq is in the regulatory review process. A small Phase IIIb trial was conducted in Thailand. No unexpected adverse reactions have been detected to date.

Closed Session: Merck & Co & Regulators

The RotaTeq Experience: Teleconference - Presenter Chris Mast

The process leading to licensure in USA and other countries was described. The current post marketing risk-management plans were outlined. These consist of post marketing surveillance and active pharmaco-vigilance studies in several countries. In the US a p-m study of 44 000 vaccinees is in progress - this is designed to detect an increased risk of IS early. In the EU there is a study in children to determine the incidence and age distribution of "natural" IS. In Nicaragua a safety and disease surveillance study plans to analyse the impact of the vaccine on disease and viral strain distribution.

RotaTeq Regulatory process in USA: Dr Rose Tiernan US FDA CBER

The regulatory review process in the USA was described in relation to RotaTeq. The clinical trials and conditions had been decided in consultation between Merck and CBER in 2000 (the IND process). Results of the Rotavirus Efficacy and Safety trial (REST) demonstrated that within 42 days of any vaccine dose, there was no increased risk for intussusception when compared to placebo i.e. relative risk 1.6 (95% CI 0.4, 6.4). However, the risk for intussusception was not zero. Dr. Tiernan pointed out that at dose #2 of RotaTeq there were more cases of

intussusception after RotaTeq for each of the time windows/day ranges assessed but that the REST trial was not designed to evaluate intussusception after each dose. RotaTeq was licensed by FDA in Feb 2006 but was required to conduct post marketing surveillance, as described above.

Table 7 from RotaTeq® label
Intussusception cases by day range in relation to dose in REST

Day Range	Dose 1		Dose 2		Dose 3		Any Dose	
	RotaTeq	Placebo	RotaTeq	Placebo	RotaTeq	Placebo	RotaTeq	Placebo
1-7	0	0	1	0	0	0	1	0
1-14	0	0	1	0	0	1	1	1
1-21	0	0	3	0	0	1	3	1
1-42	0	1	4	1	2	3	6	5

RotaTeq and Intussusception surveillance in the USA: Penina Harber CDC (by Rose Tiernan)

The CDC and FDA are responsible for following the post marketing use of vaccines in the USA. The FDA/CDC Vaccine Adverse Event Reporting System (VAERS) and CDC Vaccine Safety Datalink (VSD) post-marketing programs were described. At this time, the detected IS incidence is not above the background in this age group. Although current rates of IS in VAERS are not greater than expected, because of the data assumptions, it is not possible to completely exclude risk. U.S. post-marketing surveillance for intussusception and re-calculation of estimates is an ongoing effort.

Closed Session: GSK and Regulators.

The Rotarix experience: Dr Verstraeten

The characteristics of the vaccine were described, and process leading to registration in many countries. Continued post-marketing surveillance has shown a small cluster of IS cases following vaccination. Numbers are too small to make a judgement at this time. Several further studies of Rotarix in special population groups are in progress or planned.

EMEA Perspective: Pieter Neels EMEA CHMP

The EMEA continuing concerns with Rotarix include, mal-administration (by injection), continued surveillance for IS, studies for impact on disease incidence and viral strains in vaccinated populations, and a possible weak association with Kawasaki disease.

In the RotaTeq pre-licensure experience, Kawasaki disease has been noted. Drs. Neels and Tiernan discussed the pre-licensure case split of 5 US cases of Kawasaki disease in the RotaTeq arm to 1 case from Finland in the placebo arm. No reports of Kawasaki disease in RotaTeq recipients had been found in U.S. post-licensure data (VAERS and Vaccine Safety Datalink) to date. No Kawasaki disease cases from prior pre- or post-licensure experience with Rotashield had been noted. FDA and EMEA were planning label changes to incorporate Kawasaki disease. FDA planned to also include the serious adverse event of Kawasaki disease in the US post-marketing studies and discuss Kawasaki disease at the Advisory Committee for Immunization Practices (ACIP) in late June 2007.

Regarding the small Phase IIIb studies conducted in some countries to support the registration there is concern. If data provided to the EU can be extrapolated then the local studies are unnecessary if the data is non-extrapolatable then the small studies are inadequate. Local strain surveillance may be necessary before use of vaccine can be advocated.

Reference Articles:

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Safety and efficacy of a pentavalent human-bovine (WC3) re-assortant rotavirus vaccine.

Ruiz-Palacios G.M., et al. 2006. NEJM. **354**; 11-22.

Safety and efficacy of an attenuated vaccine against severe rotavirus gastroenteritis.

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Guidance for industry - E2E Pharmacovigilance planning.

ASA FDA CDER & CBER. March 2005

Good Pharmacovigilance practices and pharmacoepidemiologic assessment.