

# Recommendations Regarding Request for Partial Waiver of Pediatric Studies - Rotarix

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**From:**

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**Subject:** Rotarix (Rotavirus Vaccine, Live, Oral): Recommendations regarding request for partial waiver of pediatric studies

**To:** BLA STN#125265

**Through:**

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**Product Name:** Rotarix Vaccine

**Applicant Name:** GlaxoSmithKline Biologicals

**Indication:** Prevention of rotavirus gastroenteritis in infants and children.

**Statutory Reasons:**

*505.B (b)(2)(B)(i): necessary studies are impossible or highly impracticable*

*505.B. (b)(2)(B)(iii)(I): the drug or biological product -- (aa) does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in that age group; and (bb) is not likely to be used in a substantial number of pediatric patients in that age group*

**Rationale:**

GlaxoSmithKline Biologicals has requested a waiver of pediatric studies for Rotarix vaccine in children 0-5 weeks of age and in children > 26 weeks of age. As the clinical reviewer for the Rotarix BLA, I recommend that waivers be granted for these age groups. The justifications for this recommendation are described below.

**0-5 weeks of age**

A waiver of studies of Rotarix in children 0-5 weeks of age is based on the following sections of the Pediatric Research Equity Act (PREA):

*505.B (b)(2)(B)(i): necessary studies are impossible or highly impracticable*

**Justification:** It would be highly impracticable to enroll sufficient numbers of subjects 0-5 weeks of age in studies of Rotarix and inappropriate to require such studies because of

- the potential limitations of the neonatal immune response ;
- the potential for clinically significant fever and other adverse events that may be associated with vaccination of vulnerable neonates.

With the exception of hepatitis B vaccine, which is routinely administered shortly after birth, in part, to prevent unrecognized perinatal transmission of hepatitis B virus, the infant immunization program in the U.S. is initiated at a minimum of 6 weeks of age. In general, limitations of the neonatal immune response (e.g. weak and short-lived antibody response and inhibitory influence of maternal antibodies) have been significant barriers to effective immunization earlier in life.

As with all preventive vaccines, a high standard of safety would be expected for vaccines administered to healthy neonates. Moreover, the vulnerability of the neonate poses unique safety considerations for clinical studies of preventive vaccines. For example, post-vaccination fever assumes greater clinical significance in neonates than in older infants or children because of the high risk for serious bacterial infection and the difficulty in diagnosing the presence of invasive disease by physical examination and laboratory testing in the neonatal period. Hospitalization, diagnostic evaluation including cerebrospinal fluid studies, and administration of intravenous antibiotics represent the standard of care in the U.S. for febrile neonates; such interventions carry risk for iatrogenic adverse consequences. Administration of Rotarix in healthy infants 0-5 weeks of age poses at least a theoretical concern for excess fever and other adverse events due to vaccination. Among subjects from the Rotarix BLA studies that received Rotarix at the proposed licensure potency of  $\geq 10^{6.0}$  CCID<sub>50</sub> per dose and were monitored for solicited adverse events, reporting rates of fever  $\geq 100.4^{\circ}\text{F}$  within 8 days post-vaccination was 25.4% of infants after Dose 1 and 27.6% of infants after Dose 2.<sup>1</sup> Another theoretical concern is a risk for intussusception associated with vaccination as seen with a previously licensed rotavirus vaccine, Rotashield. The diagnosis of intussusception is difficult in the vulnerable neonate population and suspicion of this condition requires hospitalization and invasive diagnostic testing and attendant risk of iatrogenic adverse events.

*505.B. (b)(2)(B)(iii)(I): the drug or biological product -- (aa) does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in that age group; and (bb) is not likely to be used in a substantial number of pediatric patients in that age group*

**Justification:** Rotarix does not represent a meaningful therapeutic benefit over existing therapies for patients in 0-5 weeks of age because there are currently no recommended rotavirus vaccines or targeted anti-rotavirus drugs for this age group. In addition, rotavirus diarrhea in this age population in the U.S. is most often mild and responds well to oral rehydration therapy. In view of the potential limitations of the neonatal immune response and potential risks of neonatal vaccination as stated above, Rotarix is not likely to be used by a substantial number of infants 0-5 weeks of age.

### **25 weeks-18 years of age**

A waiver of studies of Rotarix in toddlers and adolescents is based on the following sections of the Pediatric Research Equity Act (PREA):

*505.B. (b)(2)(B)(iii)(I): the drug or biological product -- (aa) does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in that age group; and (bb) is not likely to be used in a substantial number of pediatric patients in that age group*

**Justification:** The only other U.S. licensed rotavirus vaccine, RotaTeq, is approved for use as a 3-dose series in infants 6-32 weeks of age. Rotarix would likely not represent a

meaningful therapeutic benefit over RotaTeq because these vaccines have conferred similar protection against any RV GE and against severe RV GE during the first 2 years of life, the period where severe rotavirus infections occur most commonly among pediatric patients in the U.S. Rotarix would also likely not represent a meaningful therapeutic benefit in older children because subsequent infections in this pediatric population usually result in much milder disease, as a result of anti-RV immunity developing after infections during the first 2 years of life. Rotarix is not likely to be used in a substantial number of pediatric patients who are presently as old as 2 years of age because they are expected to be vaccinated with either Rotarix from 6-24 weeks of age or RotaTeq from 6-32 weeks of age. Rotarix is also not likely to be substantially used in older pediatric ages because these patients develop much milder infections which are self-limiting, or respond well to oral rehydration therapy. Furthermore, a study in infants and children > 24 weeks of age is not needed, as data obtained from the well designed pivotal trials in infants 6 weeks to 24 weeks of age can be extrapolated to children > 24 weeks for both safety and efficacy(505B(a)(2)(B)(ii).

#### References

1. Rotarix Summary of Clinical Safety Report, page 41.