

**ROTARIX®
(Rotavirus Vaccine, Live Oral):
GSK's PCV1 Investigation**

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1

Overview

- Unexpected finding of PCV1 in Rotarix (*J Virol* 2010;84:6033)
- Confirmed by GSK mid-March
- March 22: FDA recommended temporary suspension of use pending further investigation
- 6 May: FDA notification of PCV1 and PCV2 in RotaTeq®
- 7 May: FDA VRBPAC meeting
<http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Blood/VaccinesandOtherBiologics/VaccinesandRelatedBiologicalProductsAdvisoryCommittee/vom211828.htm>
- 14 May: FDA "determined it is appropriate to resume the use of Rotarix and continue the use of RotaTeq"
- All available data support PCV1 in Rotarix is a manufacturing quality issue not a safety issue

2

Rotarix – licensed in over 110 countries



- 69 million doses distributed worldwide; 2.5 million in the US
- Manufactured in compliance with FDA regulations on adventitious agent testing, in accordance with guidance at time of licensure

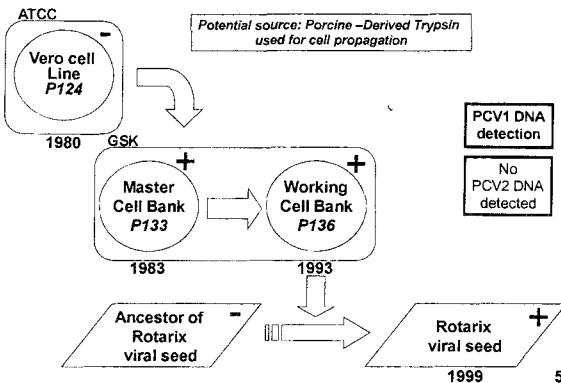
3

- PCV1 – nonpathogenic virus common in pigs
- PCV1 infection widespread in pigs
 - PCV1 not known to cause disease in pigs or any other animal including humans
 - No convincing evidence of human infection by PCV1
 - PCV1 detected in U.S. pork products

- PCV2 not found in Rotarix
- PCV2 causative agent: "postweaning multisystemic wasting syndrome" in pigs
 - PCV2 not known to cause disease in humans

4

PCV1 Detected in Starting Materials of Rotarix



5

Investigation Strategy Based on Avian Leukosis Virus Precedent

Is PCV1 signal associated with presence of:

1. Viral particles?
2. Viral particles capable of infecting permissive cells?
3. Viral particles capable of productive infection in human cells?
4. Viral particles capable of causing infection in human infants?

6

Rotarix: Manufacturing Investigation Conclusions		
Is PCV signal associated with presence of:		
Manufacturing	1. Viral particles?	YES very low amount
	2. Viral particles capable of infecting permissive cells?	YES
	3. Viral particles capable of productive infection in human cells?	NO
Clinical	4. Viral particles capable of causing infection in human infants?	

- ### Clinical Testing Objectives
- To evaluate if infants receiving 2 or 3 doses of Rotarix or placebo develop an immune response to PCV1 as assessed by the presence of antibodies against PCV1
 - To evaluate the presence of PCV1 DNA and pattern of detection in stool samples collected at pre-determined time points after a single dose of Rotarix or placebo

- ### Clinical Testing Approach
- Blinded retrospective laboratory evaluations on archived samples from completed clinical trials for Rotarix
 - Selected studies following criteria:
 - Placebo controlled
 - Collection of pre/post vaccination sera
 - Collection of stool samples (subset of subjects in Rotarix studies stool collected at days 3, 7, 10, 15, 22, 30, 45 after vaccination)
 - Samples tested from 4 completed studies
 - Conducted in Africa, Asia, Europe, Latin America
 - Infants aged 6-12 weeks at 1st dose
 - 3 studies healthy infants, 1 study HIV+ infants
 - Samples from 80 subjects (40 Rotarix, 40 Placebo)
 - Laboratory assays:
 - Serum: IPMA to detect anti-PCV1 antibody response
 - Stool: Q-PCR to detect PCV DNA

- ### Lack of evidence for PCV1 Infection in Infants
- None of the infants seroconverted
 - 4 of 40 Rotarix recipients had PCV1 in stool (2/5 [40%] at day 3, and 2/40 [5%] at day 7; none at later time points (days 10, 15, 22, 30, 45) after vaccination)
 - Adverse event profile in subjects with PCV1 DNA detected in stool was similar to placebo recipients
 - Currently available data do not support PCV1 infection in infants who received Rotarix in clinical trials

Rotarix Clinical Investigation Conclusions		
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	2. Viral particles capable of infecting permissive cells?	YES
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Clinical	4. Viral particles capable of causing infection in human infants?	NO

- ### Overview Safety and Overall Benefit:Risk
- Presence of PCV1 in Rotarix from the early stages of development
 - GSK's primary focus: patient safety
 - Rotarix safety database: large, extensive, continuously monitored
 - No specific PCV1 lens to query database

Large Global Development Program Supported US Licensure in 2008

- 11 global studies; 10 randomized, blinded, prospective, placebo-controlled
- N= 75,029: Rotarix N=40,290 Placebo N=34739
- Efficacy evaluated through 2 years/rotavirus seasons after vaccination
- Safety evaluated in all studies
 - specific study (N=63,225) powered for intussusception assessment

13

No New Safety Concerns Found by Recent FDA Pediatric Advisory Committee

- March 22, 2010 – routine safety review
- FDA conclusion: *“No new safety concerns identified...”*
- FDA recommendation: *“continued monitoring of Rotarix”*
- PAC unanimously endorsed FDA conclusion and recommendations
- Product reviewed contained PCV1

14

Large Global Postmarketing Database Supports Ongoing Safety

- Pharmacovigilance activities
 - Worldwide network for spontaneous reporting
 - Worldwide expedited regulatory agency reporting
 - Enhanced PV for intussusception
- Doses Distributed: 69 million
- 2981 Adverse Event reports
 - reporting rate 4.3/100,000 doses distributed
 - including 1177 SAE reports
 - consistent with rates expected with new vaccines

15

Post-licensure Studies Continue to Evaluate Safety and Effectiveness

- Clinical trials in select populations
 - Safety and immunogenicity in HIV positive infants
 - Safety and immunogenicity in preterm infants
 - Transmission between twins
- Post-licensure observational studies
 - Safety: Mexico, Europe, US
 - Effectiveness: worldwide

16

Rotarix is Effective in Preventing Severe Rotavirus Gastroenteritis

Country	Outcome	Effect	Journal
Australia (New S Wales)	pos. RV isolates and ED visits due to GE	lowest numbers compared to previous 8 RV seasons	Comm Dis Intell 2009
Australia (Central)	G9 RV hospitalized GE	85% Vaccine effectiveness	CID 2009
Brazil	All-cause GE hospitalization	26-48% rate reduction	PIDJ 2010
Brazil (Recife)	G2[P4] severe RV diarrhea	77% V effectiveness	JID 2010
Brazil (San Paolo)	RV GE hospitalization	59% rate reduction	ESPID 2009
El Salvador	severe RV gastroenteritis	74% V effectiveness	WHOWER 2009
Mexico	All-cause diarrhea-related mortality	41% rate reduction	NEJM 2010

17

Rotarix Benefit: Risk is Positive in Presence of PCV1

- RV leading cause of severe childhood diarrhea
- Vaccination only known effective preventative strategy
- Globally: RV vaccine use anticipated to prevent about 2 million deaths over next decade (NEJM 2010:362,4)
- US: vaccination has resulted in a 60% reduction in RV disease as compared to pre-vaccine era (MMWR 2009:58:41)
- Rotarix protects against RV GE, with safety profile comparable to placebo
- Safety data from clinical trials and postmarketing reflects presence of PCV1
- Benefit : risk for Rotarix remains highly favorable

18

Where GSK Is Now

- Ongoing discussions with FDA regarding additional clinical investigations
- GSK is committed to manufacturing PCV1-free Rotarix; developing new manufacturing process is complex and will take time
- Continue ongoing comprehensive pharmacovigilance activities
- Use of Rotarix resumed and available

19

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20